VOLUME 53 NUMBER 3 MARCH 1960

PROCEEDINGS

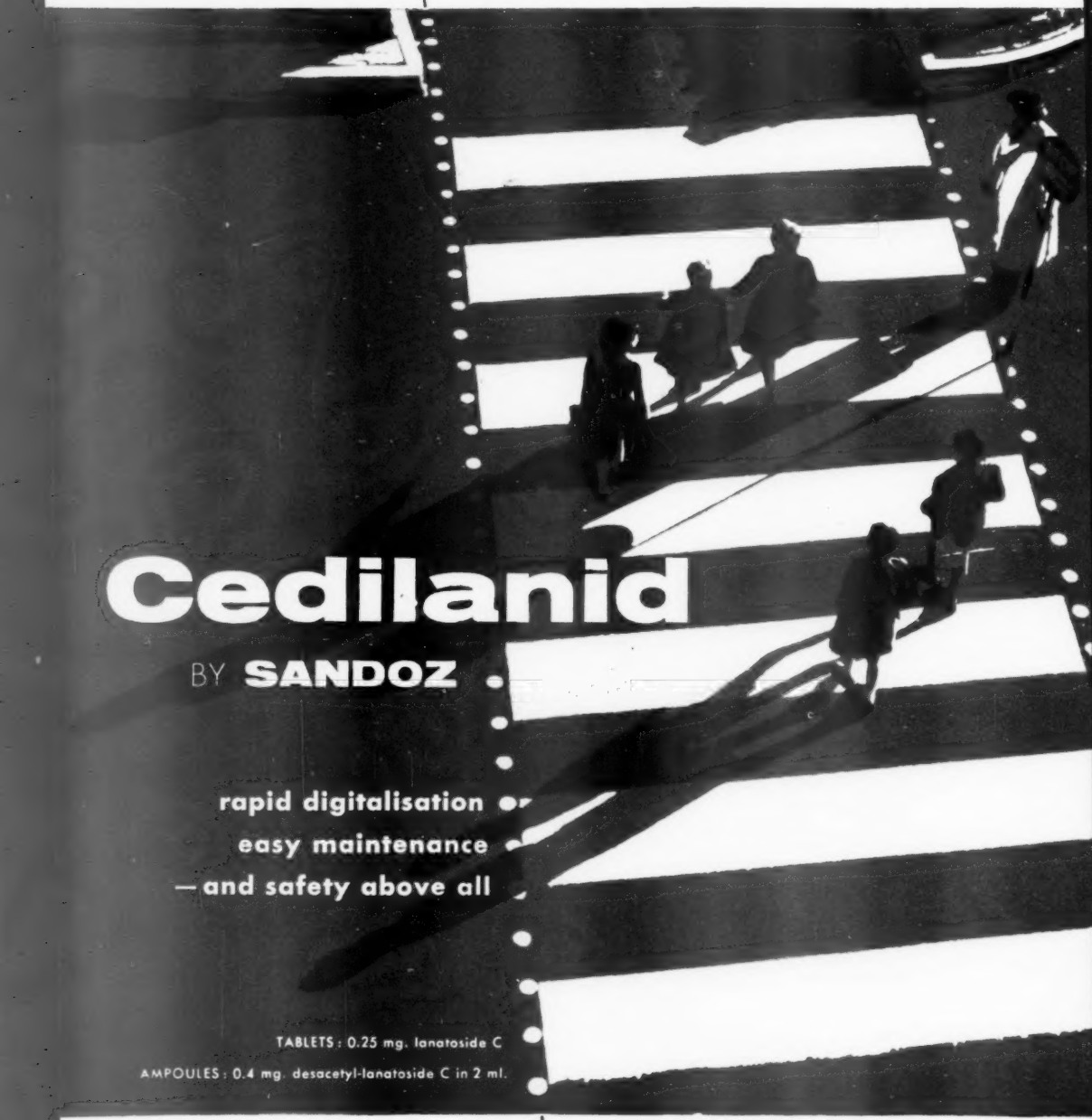
of the

ROYAL SOCIETY OF MEDICINE

Published by
THE ROYAL SOCIETY OF MEDICINE · 1 WIMPOLE STREET · LONDON · W 1

All rights reserved

In the treatment of cardiac failure ...



Cedilanid

BY **SANDOZ**

rapid digitalisation
easy maintenance
— and safety above all

TABLETS : 0.25 mg. lanatoside C

AMPOULES : 0.4 mg. desacetyl-lanatoside C in 2 ml.

"...Cedilanid is probably safest of all"

— *British Encyclopaedia of Medical Practice*, **6**, 407

VOLUME 53 NUMBER 3 MARCH 1960

PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

ISSUED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE

HONORARY EDITORS

SELWYN TAYLOR R. I. S. BAYLISS

EDITORIAL REPRESENTATIVES OF SECTIONS

O. P. DINNICK (Anæsthetics)
RICHARD ASHER (Clinical)
A. C. CUNLIFFE (Comparative Medicine)
P. D. SAMMAN (Dermatology)
N. F. MACLAGAN (Endocrinology)
J. C. McDONALD (Epidem. and Preventive Med.)
A. C. WHITE (Exper. Med. and Therap.)
DAVID WHEATLEY (General Practice)
W. H. McMENEMEY (History of Medicine)
F. C. W. CAPPS (Laryngology)
PHILIP ELLMAN (Medicine)
MACDONALD CRITCHLEY (Neurology)
JOSEPHINE BARNES (Obstetrics and Gynæcology)
J. H. HOVELL (Odontology)
S. J. H. MILLER (Ophthalmology)
J. A. CHOLMELEY (Orthopædics)
G. H. BATEMAN (Otology)
D. MacCARTHY (Pædiatrics)
B. W. LACEY (Pathology)
A. C. BOYLE (Physical Medicine)
HAROLD DODD (Proctology)
J. S. PIPPARD (Psychiatry)
A. M. RACKOW (Radiology)
D. H. PATEY (Surgery)
Surg. Cdr. F. P. ELLIS (United Services)
A. CLIFFORD MORSON (Urology)

ASSISTANT EDITOR

D. LUKYN-WILLIAMS

SECRETARY OF THE ROYAL SOCIETY OF MEDICINE

R. T. HEWITT

All correspondence to
THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1
(Tel.: LANgham 2070)

Distributing Agents:
H. K. LEWIS & CO. LTD., 136, GOWER STREET, LONDON, W.C.1

In the U.S.A.:
GRUNE & STRATTON, INC., 381, FOURTH AVENUE, NEW YORK, 16

Advertisement Managers:
H. S. JANES & PARTNERS LTD., 99, GOWER STREET, LONDON, W.C.1
Telephone: EUSton 3221

Monthly, 10s. 6d. net. Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.

FOR PATIENTS WHO 'FEEL ROTTEN' ···VILLESCON

after illness

Villescon is the first tonic truly capable of restoring vitality to 'run down' patients. They find apathy and fatigue replaced by renewed interest in life and an inclination to greater activity and movement.

Villescon's action increases respiratory rate and volume, stimulates the appetite in most cases, and promotes a beneficial back-to-normal sense of physical and mental well-being.

Villescon can be prescribed whenever a tonic is indicated. *Villescon is contra-indicated in the presence of thyrotoxicosis.*

4534

FOR EVERY TONIC PRESCRIPTION VILLESCON

VILLESCON*

1-phenyl-2-pyrrolidino-pentane hydrochloride, with vitamins

THE FIRST TRUE TONIC

Manufactured and distributed in the U.K. by Pfizer Ltd., Folkestone, Kent for C. H. BOEHRINGER SOHN, INGELHEIM am RHEIN

Registered proprietors of the Trade Mark. **Regd. Trade Mark.*

PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

Vol. 53 No. 3 March 1960

CONTENTS

	Whole Proceedings Page
Section of Otology	
Some Thoughts on the Eustachian Tube. President's Address by RONALD MACBETH, D.M., F.R.C.S.	151
Books Received for Review	162
Section of Laryngology	
The Maxillary Sinus. President's Address by MYLES L. FORMBY, F.R.C.S.	163
Section of Surgery	
October 7, 1959	
List of Films shown	169
November 4, 1959	
DISCUSSION ON EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF MALIGNANT DISEASE	169
December 2, 1959	
List of Specimens shown	176
Section of Experimental Medicine and Therapeutics	
THE MEASUREMENT OF BLOOD GAS TENSIONS	177
Measurement of Blood Oxygen Tension. J. M. BISHOP, M.D., M.R.C.P. ..	177
Measurement of Blood Carbon Dioxide Tension. J. F. NUNN, PH.D., F.F.A. R.C.S. ..	180
Section of Anæsthetics	
Anæsthesia in Dystrophia Myotonica [*Abridged*]—A Review of the Hazards of Anæsthesia. Registrar's Prize Essay by LEON KAUFMAN, M.B., F.F.A. R.C.S. ..	183

	Whole Proceedings Page
Section of Ophthalmology	
November 12, 1959	
Paper (*By Title*)	189
December 10, 1959	
Forum	189
January 14, 1960	
Congenital Abnormalities of the Eye with Particular Reference to Prematurity. C. A. BROWN, F.R.C.S., D.O.M.S. ..	189
Binocular Vision in Bilateral Aphakia. N. L. STOKOE, D.O., F.R.C.S.ED. ..	192
The Visual Prognosis in Still's Disease with Eye Involvement. W. K. SMILEY, D.O.M.S., F.R.C.S. ..	196
Section of Pathology	
October 20, 1959	
List of Papers read	197
November 3, 1959	
SYMPOSIUM ON ENZYME SYSTEMS IN DIAGNOSIS	197
November 17, 1959	
LABORATORY MEETING AT THE CENTRAL PUBLIC HEALTH LABORATORY, COLINDALE AVENUE, LONDON. List of Demonstrations given ..	202

Continued overleaf

CONTENTS (*continued*)

	Whole Proceedings Page
Section of Physical Medicine	
November 11, 1959	
The Blood Supply of the Brachial Plexus. SAJIDA ABDULLAH, M.SC., M.B., and RUTH E. M. BOWDEN, D.SC., M.B.	203
Steroid Osteoporosis [*Abridged*]. P. HUME KENDALL, M.R.C.P., D.PHYS.MED.	206
Early Radiographic Signs of Rheumatic Disease. A. C. YOUNG, M.B., D.M.R.D. ..	208
December 9, 1959	
MEETING IN THE DEPARTMENT OF PHYSICAL MEDICINE, HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, LONDON. List of Cases shown	210
Section of General Practice	
DISCUSSION ON CO-OPERATION IN GENERAL PRACTICE	211
Books Recently Presented and Placed in the Society's Library	216
Section of Endocrinology	
CASES	217-222
Clinical Section	
November 13, 1959	
CASES	223-227
December 11, 1959	
CASES	228-230
Book Reviews	231

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors, Royal Society of Medicine . . . . The copyright of all papers presented at meetings by Fellows of the Society or Members of the Sections (other than those which have been previously published) shall be deemed to be the property of the Society until a decision has been made by the Society in regard to their publication.

In light diets . . .

In light diets, as well as under more normal regimes, Lucozade fulfils a most valuable role, not only in abating thirst and protecting the mucosa of the mouth, but also in arousing the appetite and contributing to the retention of more solid food. Lucozade is especially useful in the diet of patients in whom nausea of pregnancy, dehydration, or other special conditions make it necessary to supply an easily tolerated, nutritious fluid intake.

Lucozade is lightly carbonated with an attractive golden colour and a pleasant citrus flavour. It contains 23.5% w/v Liquid Glucose and its energy value is 21 Calories per fluid ounce. It is supplied in 6 oz. and 26 oz. bottles.

LUCOZADE

THE TROUBLE WITH SECURITY...

...IS THAT ONE CAN NEVER BE SURE OF IT LASTING

Supposing you were ill for a considerable time. Would your practice and consequently your income suffer? This Society, run by Doctors for Doctors, specialises in Insurance for the Medical Profession.

Non Cancellable With Profit SICKNESS AND ACCIDENT INSURANCE
LIFE ASSURANCE • PERSONAL PENSION POLICIES

When you are buying a car why not ask for details of the Hire Purchase Scheme of our subsidiary company — the Medical Sickness Finance Corporation of 7 Cavendish Square, London, W.1. Telephone Museum 9348.

MEDICAL SICKNESS ANNUITY AND LIFE ASSURANCE SOCIETY LIMITED

Write for particulars, mentioning this advertisement.

3 CAVENDISH SQUARE, LONDON, W.1

Telephone Langham 0341

British Pharmaceutical Codex

1959

The seventh edition of the British Pharmaceutical Codex, just published, provides the latest available information on the properties, standards, actions and uses, contraindictions, dosage and formulation of nearly 1000 medicinal substances in current use.

There are **70 new monographs — 78 new formulæ — 3 new appendixes**

The Codex has been compiled by the aid of ten committees and sub-committees on which over 100 experts in their particular sphere have served. In addition approximately 50 specialists have prepared and commented on proposed new and amended formulæ.

Pp. xxix+1301. *Price* 70*s*. (*Packing and postage* 2*s*. 6*d*., *overseas* 4*s*.)

THE PHARMACEUTICAL PRESS

17 Bloomsbury Square, London, W.C.1

A History of Medicine

Revised Edition *by* **DOUGLAS GUTHRIE**

'Many histories of medicine have appeared in recent years, but no post-war work in a single volume is better than this one by Dr. Douglas Guthrie. It is distinguished by its comprehensive scope and attractive style . . . combined with this easy literary style is evidence of extensive bibliographical research and of a scholarly enthusiasm for accuracy. . . . It would be hard to suggest how this excellent and reasonably priced book could be improved.'—*Lancet*.

72 *half tone plates* $8\frac{3}{4} \times 5\frac{5}{8}$ *xvi* + 464 *pp* 42*s*

HISTORY OF THE ROYAL MEDICAL SOCIETY

1737—1937 *by* **JAMES GRAY MA FRSE**

This is the first detailed history of the oldest medical society in Great Britain from the time of its foundation until the bicentenary celebrations in 1937.

Illustrated *Edinburgh University Press* 42*s*

Prospectuses available from 36 Park Street London W1

NELSON

★ *Some Recent Publications from E. and S. Livingstone* ★

EMERGENCIES IN MEDICAL PRACTICE
Sixth Edition. Edited by C. ALLAN BIRCH, M.D., F.R.C.P.
763 *pages.* 162 *illustrations.* **45s.**

A SHORT SYNOPSIS OF HUMAN PROTOZOOLOGY AND HELMINTHOLOGY
By L. R. S. MacFARLANE, *O.B.E.*, M.D., M.A., D.P.H.
260 *pages.* 183 *illustrations.* **35s.**

PROCEEDINGS OF A SYMPOSIUM ON IMMUNIZATION IN CHILDHOOD.
Held in London, May, 1959
Edited by D. A. CANNON, *O.B.E.*, W. C. COCKBURN, D. G. EVANS and H. J. PARISH.
140 *pages.* 5 *illustrations.* **17s. 6d.**

AN INTRODUCTION TO PHARMACOLOGY
By J. J. LEWIS, M.Sc.
838 *pages.* 183 *illustrations.* **55s.**

THE ROYAL EDINBURGH HOSPITAL FOR SICK CHILDREN, 1860-1960
By DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed.
88 *pages.* 40 *illustrations.* **17s. 6d.**

SURGERY OF REPAIR AS APPLIED TO HAND INJURIES
Second Edition. By B. K. RANK, *C.M.G.*, M.S. (Melb.), F.R.C.S., F.R.A.C.S., and A. R. WAKEFIELD, M.S.(Melb.), F.R.C.S., F.R.A.C.S.
298 *pages.* 486 *illustrations.* **45s.**

OSTEOCHONDRITIS DISSECANS.
Loose Bodies in Joints: Etiology, Pathology, Treatment
By I. S. SMILLIE, *O.B.E.*, Ch.M., F.R.C.S.Ed.
232 *pages.* 242 *illustrations.* **60s.**

OUTLINE OF ORTHOPÆDICS
Third Edition. By JOHN CRAWFORD ADAMS, M.D., F.R.C.S.
448 *pages.* 368 *illustrations.* **35s.**

THE CELL OF SCHWANN
By GILBERT CAUSEY, M.B., F.R.C.S.
132 *pages.* 55 *illustrations.* **21s.**

FRACTURES AND JOINT INJURIES
Fourth Edition, Third Reprint. By SIR REGINALD WATSON-JONES. In two volumes.
1,130 *pages.* 1,613 *illustrations.* **£6 10s.**

E. & S. LIVINGSTONE, LTD., TEVIOT PLACE, EDINBURGH

NEW CHURCHILL BOOKS

New (Second) Edition. **THE HAEMOLYTIC ANAEMIAS** *In Two Parts.*
By J. V. DACIE, M.D., F.R.C.P.
Part 1. **Congenital Anæmias.** 118 illustrations. **45s.** *Just ready.*
Part 2. **Acquired Anæmias.** *In preparation.*

LEUKÆMIA: Research and Clinical Practice
By F. G. J. HAYHOE, M.A., M.D., M.R.C.P.
12 Coloured Plates and 196 Black and White Illustrations.
Ready this month. **80s.**

INDUSTRIAL PULMONARY DISEASES
A Symposium edited by E. J. KING, Ph.D., D.Sc., F.R.I.C., and C. M. FLETCHER, *C.B.E.*, M.A., M.D., F.R.C.P.
98 Illustrations. *Ready April.* **32s.**

DEAFNESS
By J. C. BALLANTYNE, F.R.C.S., D.L.O.
71 Illustrations. *Ready next month.* **25s.**

pH AND BLOOD GAS MEASUREMENT: Methods and Interpretation
A Symposium edited by R. F. WOOLMER, *V.R.D.*, B.A., B.M., B.Ch., F.F.A.R.C.S.
48 Illustrations. **30s.**

Latest 'Recent Advances'

CLINICAL PATHOLOGY: Bacteriology; Chemical Pathology; Hæmatology; Histology
Edited by S. C. DYKE, D.M., F.R.C.P.
New Issue—Series 3. 151 Illustrations. *Ready this month.* **50s.**

SURGERY
Edited by SELWYN TAYLOR, M.A., D.M., M.Ch., F.R.C.S.
New (Fifth) Edition. 160 Illustrations. **60s.**

PUBLIC HEALTH
By J. L. BURN, M.D., D.P.H.
New (Second) Edition. 54 Illustrations. **40s.**

PRACTICAL PROCEDURES IN CLINICAL MEDICINE
Biochemical and Radiological Investigations
By R. I. S. BAYLISS, M.A., M.D., F.R.C.P.
New (Third) Edition. 54 Illustrations. **42s.**

A PRACTICE OF GENERAL ANÆSTHESIA FOR NEUROSURGERY
By R. I. W. BALLANTINE, M.R.C.S., L.R.C.P., D.A., F.F.A.R.C.S. With the collaboration of IAN JACKSON, M.R.C.S., L.R.C.P., D.A.
68 Illustrations. *Ready April.*

FRACTURES, DISLOCATIONS AND SPRAINS
By PHILIP WILES, M.S., F.R.C.S., F.A.C.S.
519 Illustrations. *Ready next month.* **27s. 6d.**

A TEXTBOOK OF SURGICAL PATHOLOGY
By C. F. W. ILLINGWORTH, *C.B.E.*, M.D., Ch.M., F.R.C.S.(Edin.), and BRUCE M. DICK, M.B., F.R.C.S.(Edin.).
New (Eighth) Edition. 329 Illustrations. *Ready shortly.* **75s.**

Latest from U.S.A.

ARTHRITIS: General Principles, Physical Medicine and Rehabilitation
Edited by E. W. LOWMAN, M.D.
134 Illustrations. **68s.**

BACK PAIN: Diagnosis and Treatment Using Manipulative Techniques
By J. McM. MENNELL, M.A., M.B., B.Chir., D.M.R.E.
78 Illustrations. **68s.**

CANCER AND ALLIED DISEASES OF INFANCY AND CHILDHOOD
By I. M. ARIEL, M.D., F.A.C.S., and G. T. PACK, M.D., F.A.C.S.
318 Illustrations. **160s.**

J. & A. CHURCHILL LTD., 104 GLOUCESTER PLACE, LONDON, W.1

The World's Greatest Bookshop

FOYLES

* * FOR BOOKS * *

FAMED CENTRE FOR MEDICAL BOOKS

"A bookshop such as booklovers dream of. There is no other bookshop, anywhere, to compare with Foyles." —*A Customer's Letter.*

FOYLES TRAVEL BUREAU
Railway tickets and reservations at station prices

119-125 CHARING CROSS ROAD WC2

Gerrard 5660 (20 lines) ★ *Open 9-6 (including Saturdays)*

Two minutes from Tottenham Court Road Station

HMSO

MEDICAL RESEARCH COUNCIL

Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants

B. LEVIN, HELEN M. M. MACKAY, CATHERINE A. NEILL, V. G. OBERHOLZER AND T. P. WHITEHEAD

This clinical and biochemical study presents new data on rates of gain in weight, and on serum protein levels of infants of different birth weights. Values for total protein, albumin, and globulin in serum are submitted as standards of normal for full term infants.

Special Report Series No. 296
Price 16s. *(post 7d.)*

From the Government Bookshops
or through any bookseller

HMSO

The perfect drink for every occasion

JOHNNIE WALKER
Fine Old Scotch Whisky
BORN 1820—STILL GOING STRONG

We are proud . . .

to be recognized insurance agents for the medical and dental professions and proud, too, of our record of service for well over half a century.

The foundation of this service is expert, unbiased advice which is available on any insurance problem—LIFE, PENSION, SICKNESS, MOTOR CAR, HOUSEHOLD, EDUCATION.

Premiums are, in most cases, subject to substantial rebates and *all* the Agency's surplus is donated to the medical and dental charities.

The Agency can also help in negotiating LOANS for the purchase of a House, Equipment or a Motor Car.

Medical Insurance Agency Ltd.

Chairman: James Fenton, C.B.E., M.D., M.R.C.P. Gen: Manager: A. N. Dixon, A.C.I.I.

B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1

Telephone: EUSTON 6031 (9 lines)

Branches also at Birmingham - Bristol - Cardiff - Dublin - Edinburgh - Glasgow Leeds - Manchester - Newcastle upon Tyne - Southampton

★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★

Vintage 1959

Reports of the 1959 vintage were exaggerated in the Press, who, as early as Midsummer 1959, were predicting the success of the vintage. Some vineyards have produced excellent wine but several proprietors experienced difficulties because of the weather at the time of the gathering and the high sugar content in the grapes. Thanks to the activities of speculators, prices are inflated. But do not worry! We still have some of the 1955 vintage Clarets and 1957 vintage Red Burgundies to offer at sensible prices!

	Per dozen bottles
Château Meyney (St. Estèphe) 1955	136/-
Château Batailley (Pauillac) 1955	160/-
Beaune 1957	136/6
Nuits St. Georges, Les Pruliers 1957	150/-
Chambolle-Musigny, Les Charmes 1957	155/-

Would you like a copy of our WINE NEWS? Please ask for this and our lists of other offers

HEDGES & BUTLER LTD.

22 The Arcade, Bournemouth — or — 153 Regent St., London, W.1

Telephone:

Bournemouth 20943 — REGent 4444

★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★

MARMITE

yeast extract

contains

Riboflavin (vitamin B_2) 1·5 mg. per oz.
Niacin (nicotinic acid) 16·5 mg. per oz.

In Geriatrics

The opinion has been expressed that the need for vitamins, especially those of the B complex, is increased in frail elderly persons. These essential nutrients seem to exert a beneficial effect even when the diet appears to be adequate. Marmite is a yeast extract containing most of the known factors of the vitamin B group; it can easily be incorporated in the diet and is economical to use.

MARMITE LIMITED

35, SEETHING LANE, LONDON, E.C.3

5506

"BARBITURATE DEATHS INCREASING"

Under this warning headline British Medical Journal, in an editorial of October 17th, 1959, draws attention to the increasing number of deaths by poisoning, once again emphasising "that barbiturates are the most prominent group of drugs causing these deaths." How great the increase has been in recent years can be seen from the latest available figures, which show that 75% of suicidal deaths due to drugs and 80% of all accidental deaths by poisoning are caused by barbiturates. From these facts it is evident, the article concludes, that the barbiturates present a hazard that the existing precautions against overdosing have not overcome and that "*the increasing number of these deaths would suggest that something more is needed.*"

'DISTAVAL'
TRADE MARK
NON-BARBITURIC

Brand of α-phthalimidoglutarimide (thalidomide).

DC(B)L

THE DISTILLERS COMPANY (Biochemicals) LIMITED
Broadway House, The Broadway, Wimbledon, London, S.W.19
Telephone: LIBerty 6600

Owners of the trade mark 'Distaval'

A SAFE ALTERNATIVE

A letter to the British Medical Journal (October 3rd, 1959) from a General Practitioner, suggests that the new non-barbituric drug 'Distaval' seems to be "a satisfactory sedative and hypnotic in many patients" and that its use "might go a long way towards reducing the present annual mortality from overdoses of the central nervous system depressants currently prescribed." In support of this view the writer gives the following case history:

A 70-year-old man, suffering from insomnia associated with mild senile dementia, took twenty-one 100mg. tablets by mistake. No specific treatment was given, there was no vomiting or evidence of respiratory or cardiac depression. After 12 hours apparently normal sleep the patient woke up, remaining a little drowsy for a further 24 hours.

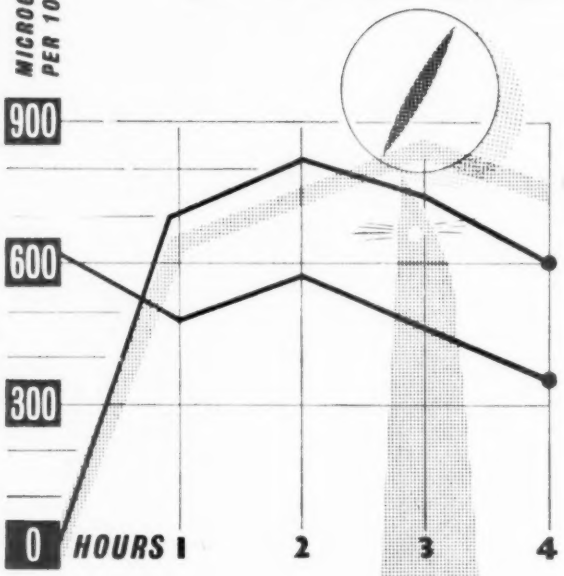
Since the introduction of 'Distaval' two years ago a number of reports have been received of cases of gross overdosing with similarly harmless results. On the other hand, no severe toxic effects of any kind have been reported.

SAFE and effective

SEDATIVE AND HYPNOTIC

DOSAGE: As a sedative ADULTS, one 25mg. tablet 2 or 3 times a day. INFANTS & CHILDREN, half to one 25mg. tablet 1 to 3 times a day.
As a hypnotic at bedtime. ADULTS 50mg. to 200mg. INFANTS & CHILDREN, 25mg. to 50mg.

REACH THE PEAK WITH THEODROX



In 'Theodrox' tablets, aluminium hydroxide protects aminophylline from breakdown by gastric enzymes to prevent theophylline irritation of stomach mucosa.

When oral aminophylline is indicated 'Theodrox' is—

EFFECTIVE High theophylline blood levels are readily attained by the oral route.

ECONOMICAL Basic weekly cost of treatment may be as little as 2/- to N.H.S.

WELL-TOLERATED Gastric irritation is negligible even at abnormally high dosage. (Four to eight tablets daily are usually sufficient.)

When mild sedation is desirable— 'Theodrox' with Phenobarbitone (gr. ¼) tablets are available.

PACKS Tablets in containers of	'THEODROX'	'THEODROX' WITH PHENOBARBITONE
25	3/-	3/6
100	9/-	9/4
1000	71/4	74/-

'THEODROX' (British Patent: 727,831) is a registered trade mark of:

RIKER LABORATORIES LIMITED

LOUGHBOROUGH • LEICESTERSHIRE

RIKER

Without it your emergency bag is incomplete

for IMMEDIATE use in:

STATUS ASTHMATICUS · ACUTE HAY FEVER · ALLERGIC EMERGENCIES
TRAUMATIC SHOCK · EMERGENCY SURGERY · FULMINATING INFECTION

—and for immediate relief (injected locally) in Rheumatoid Arthritis and Acute Bursitis

Injection 'CODELSOL' is a sterile *solution* (not a suspension) of prednisolone 21-phosphate READY FOR IMMEDIATE INJECTION, *intravenously*, *intramuscularly* or *intrasynovially*, without further mixing or dilution.

Since refrigeration is not required Injection 'CODELSOL' can be carried in your bag, ready for immediate use.

Injection 'CODELSOL' may be administered through a small-bore needle; response is very rapid and an adequate dose is contained in a small volume of solution.

Injection 'CODELSOL' may be life-saving in YOUR patient.

How supplied: Injection 'CODELSOL' is supplied in 2 ml. vials containing 20 mg. prednisolone 21-phosphate per ml.

The United Kingdom N.H.S. basic cost is 21s. 0d. per 2 ml. vial.

Literature will gladly be sent on request.

Injection 'CODELSOL'
Regd.

(PREDNISOLONE 21-PHOSPHATE, Sterile Solution of Prednisolone)

MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS

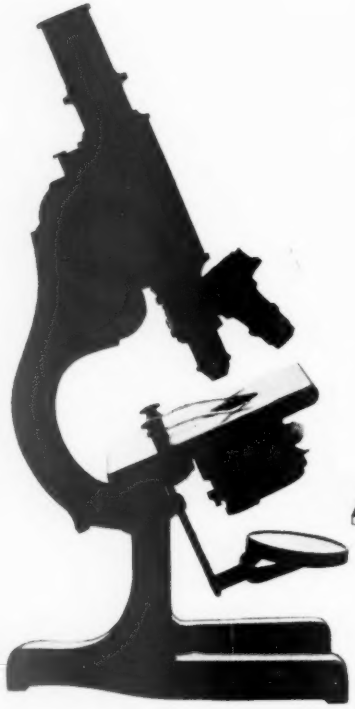
MSD

IN THE TREATMENT OF LEUKAEMIA AND

Malignant Disease

Degranol* is a cytostatic agent of a relatively low toxicity.
It is of particular value in the management of malignant disease of the haemopoietic and lymphatic systems.
It is also suggested as a prophylactic for pre- and post-operative treatment to prevent the recurrence and distribution of malignant cells.
Objective and subjective improvement have also been obtained in many cases of inoperable cancer.

References: B.M.J. *No. 5146, 22nd Aug. 1959*
LANCET, *9th May, 1959.*



DEGRANOL TRADE MARK

Mannomustine (B.C.M.)
1, 6-bis (β-chloroethylamino) - 1, 6 desoxy-D-mannitol-dihydrochloride

Packings of ampoules of 50 mg., for intravenous injection.
Available under N.H.S.

LEDA Chemicals Ltd.,
Berk House, PLO. Box 500, Portman Square, W.1.
Telephone: HUNter 6688

Sole distributors for Chinoin, Budapest

LD3

A new advance in the treatment of all types of **depression**

NARDIL

TRADE MARK

phenelzine

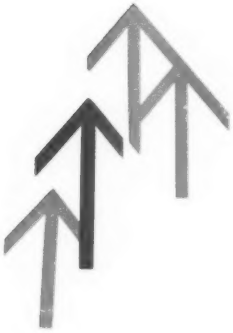
a notably safe and effective monoamine oxidase inhibitor which compares in scope and effect with **E.C.T.**

Nardil is a major advance in psychological medicine, presenting the possibility of replacing E.C.T. in the treatment of depression.

Nardil modifies the biochemical basis of depression by regulating the enzyme which destroys 5-hydroxytryptamine. This is in contrast to the amphetamine-like substances which merely mask the symptoms without influencing the underlying cause.

Nardil is indicated for all potential E.C.T. patients; for patients not responding to, or unsuitable for, E.C.T. and for those who have relapsed after E.C.T.

In clinical trials involving many thousands of patients, excellent results have been obtained with minimal side effects: and most important, with no toxic effects on blood or liver.



Response to Nardil is seen within the first week, and often within the first few days. Nardil abolishes symptoms in from 2 to 5 weeks and recovery is maintained for long periods after treatment has ceased.

Dosage schedule is simple and flexible—for inpatients one tablet three times a day and one at bedtime; for outpatients, one tablet three times a day.

Nardil is now available in bottles of 100 and 500 sugar-coated tablets each containing 15 mg. phenelzine.

Comprehensive technical information available on request.

Bibliography

Amer. J. Physiol (1953) 175, 157. J. Physiol (1954) 126, 596. 5-hydroxytryptamine, Proc. (1957) discussion p. 60. Pergamon Press. 4 Papers presented at a conference on Amine Oxidase Inhibitors, New York Academy of Sciences. November 1958. Dis. nerv. Syst. (1959) 22, 197. Amer. J. Psychiat. (1959) 116, 71.

NARDIL a safe, effective anti depressant

an original discovery of Warner Research

WILLIAM R. WARNER & CO. LTD., EASTLEIGH, HANTS.

NAR 431

TRIPLE-ACTION OINTMENT

BUCCAL TABLETS

LYOPHILISED INTRAMUSCULAR

CONTROLS INFLAMMATION
RELIEVES PAIN
PROMOTES HEALING

ARMOUR

at any site

CHYMAR

CHYMOTRYPSIN

BENEFICIAL in the management of accidental, surgical, gynaecological trauma; inflammatory skin and eye diseases; respiratory and gastro-intestinal tract inflammations; thrombophlebitis; and any conditions where inflammation, swelling and pain hinder healing.

ARMOUR PHARMACEUTICAL COMPANY LTD

EASTBOURNE · ENGLAND

AMPHETONE

REGISTERED TRADE NAME

A GENERAL STIMULANT FOR THE CENTRAL NERVOUS SYSTEM

For cases requiring a quick-acting general stimulant without increasing the patient's appetite, we consider Amphetone unique. It combines for the first time, Dexamphetamine Sulphate and Strychnine with Glycerophosphates and members of the Vitamin B Group. The Dexamphetamine provides the convalescent with an immediate feeling of well-being, this being followed by the well-known tonic effects of the other medicaments. Clinical reports have been excellent.

FORMULA

Dexamphetamine Sulphate B.P.C., 1/12 grain; Strychnine Hydrochloride B.P., 1/60 grain; Calcium Glycerophosphate B.P.C., 2 grains; Sodium Glycerophosphate B.P.C., 2 grains; Aneurine Hydrochloride B.P., 1/30 grain; Nicotinamide B.P., 1/4 grain; Riboflavin B.P., 1/60 grain; Syrup of Blackcurrant B.P.C., 2 fluid drms.; Water to 1/2 fluid ounce.

POISON | S4

Available in bottles containing 10, 20, 40, 80 fl. oz.
Prices: 4/9, 8/9, 15/6, 27/9 each, exempt from tax. Basic N.H.S. prices

JAMES WOOLLEY, SONS & CO. LTD., VICTORIA BRIDGE, MANCHESTER 3
In Association with J. C. Arnfield & Sons Limited

London Stockists: May, Roberts & Co., Ltd., 47 Stamford Hill Road, London, N.16
Distributors for Northern Ireland: Messrs. Dobbin & Stewart, 47-49 Earl Street Belfast.

for your epileptic patients

life can be normal with Trinuride

Trinuride helps the epileptic to lead a life fully active in every way, mentally as well as physically. Trinuride is often more effective in controlling epileptic seizures—and is almost entirely free from the drowsiness so often caused by other forms of treatment. Indicated in all epileptic conditions, Trinuride is especially useful in cases of grand mal and temporal lobe epilepsy. When you prescribe Trinuride you know that your patients are not progressively sinking, year by year, into a state of meaningless lethargy.

Trinuride is Phenylethylacetylurea	0.200 G
together with optimum amounts of	
Diphenyl hydatoin	0.040 G
Phenobarbitone	0.015 G

Trinuride

tablets in containers of 100 and 500 (Dispensing pack)

Bengue & Co Ltd

Mount Pleasant Wembley Middlesex

BG5

RIDDOSEDD TABLETS

A Compound of SODIUM-DIETHYLBARBITURATE-PHENACETIN-CODEINE The ideal HYPNOTIC, SEDATIVE, SOPORIFIC and ANALGESIC

- **RIDDOSEDD** induces a calm, natural sleep of several hours without any resulting somnolence.
- **RIDDOSEDD** has no injurious effects upon the heart, circulation, kidneys or respiration.
- **RIDDOSEDD** is timed to set in when patients awake during the early hours of the morning, thus ensuring a continuation of normal sleep.
- **RIDDOSEDD** as a soporific is 20 times greater than that of Sodium Diethylbarbiturate.
- **RIDDOSEDD** has proved to be a most reliable and best tolerated soporific and sedative for more than twenty years.

PACKED IN BOTTLES OF 20 and 100
Please write for details to:—

Sole Manufacturers:

RIDDELL PRODUCTS LIMITED

RIDDELL HOUSE, 10-14 DUNBRIDGE STREET, LONDON, E.2
Telephone: SHOreditch 7254. Telegrams: Pneumostat, Beth, London

BRANCH OFFICE: 11 Mansfield Chambers, St. Ann's Square, Manchester 2

ST. ANDREW'S HOSPITAL

FOR NERVOUS AND MENTAL DISORDERS

NORTHAMPTON

President—THE EARL SPENCER
Medical Superintendent—THOMAS TENNENT, M.D., F.R.C.P. D.P.H., D.P.M.

This Registered Hospital is situated in 130 acres of park and pleasure grounds. Informal and voluntary patients, who are suffering from incipient mental disorders or who wish to prevent recurrent attacks of mental trouble, temporary patients, and certified patients of both sexes are received for treatment. Careful clinical, biochemical, bacteriological and pathological examinations. Private rooms with special nurses, male or female, in the hospital or in one of the numerous villas in the grounds of the various branches, can be provided.

WANTAGE HOUSE

This is a Reception Hospital in detached grounds with a separate entrance, to which patients can be admitted. It is equipped with all the apparatus for the complete investigation and treatment of mental and nervous disorders by the most modern methods: insulin treatment is available for suitable cases. It also contains laboratories for biochemical, bacteriological and pathological research. Psychotherapeutic treatment is employed when indicated.

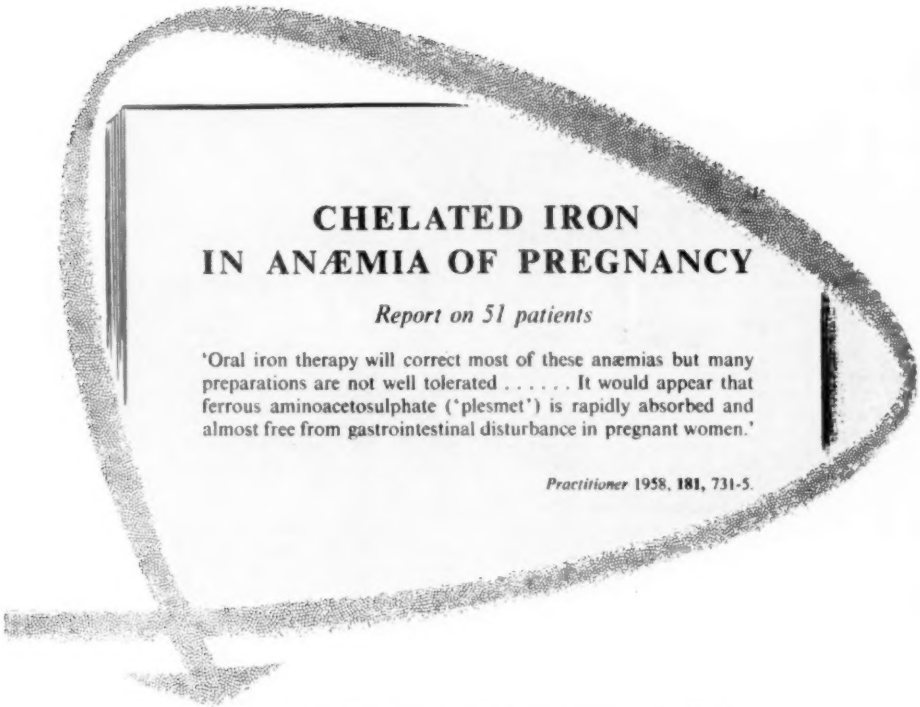
MOULTON PARK

Two miles from the Main Hospital there are several villas situated in a park and farm of 600 acres. Milk, meat, fruit and vegetables are supplied to the hospital from the farm, gardens and orchards of Moulton Park. Occupational Therapy is a feature of this branch, and patients are given every facility for occupying themselves in farming, gardening and fruit growing.

BRYN-Y-NEUADD HALL

The seaside home of St. Andrew's Hospital is beautifully situated in a park of 330 acres, at Llanfairfechan, amidst the finest scenery in North Wales. On the north-west side of the estate a mile of sea-coast forms the boundary. Patients may visit this branch for a short seaside change or for longer periods. The hospital has its own private bathing house on the seashore. There is trout-fishing in the park.

For terms and further particulars apply to the Medical Superintendent (TELEPHONE No. 34354 Northampton) who can be seen in London by appointment.



CHELATED IRON IN ANÆMIA OF PREGNANCY

Report on 51 patients

'Oral iron therapy will correct most of these anæmias but many preparations are not well tolerated . . . . . It would appear that ferrous aminoacetosulphate ('plesmet') is rapidly absorbed and almost free from gastrointestinal disturbance in pregnant women.'

Practitioner 1958, **181**, 731-5.

In the trial referred to above, excellent responses were obtained with PLESMET—the Ferrous aminoacetosulphate 'chelate' complex which minimizes oxidation and ensures maximum assimilation with a high degree of toleration.

Attention was also drawn to the low prescription cost and effective haemoglobin levels reached in the early weeks of treatment, the latter being better than the results obtained in pregnancy with other iron compounds.

Plesmet

Syrup—Palatable blackcurrant flavour without 'iron' taste, each teaspoonful equivalent to 25 mg. Ferrous Iron with 1 mg. Aneurine Hydrochloride B.P. (2 oz. bottles — 2/- ; 40 oz. bottles — 18/-)

Basic N.H.S. Price

Tablets—Each equivalent to 50 mg. Ferrous Iron with 1 mg. Aneurine Hydrochloride B.P. (Bottles of 100 — 2/8 ; Bottles of 1000 — 17/6)

COATES & COOPER LTD.

PYRAMID WORKS, WEST DRAYTON, MIDDX.

REALLY GOOD LIGHTING

The G.V.D. SYSTEM, because of the fewer fittings necessary to light a given area, is cheaper to instal, to maintain and to re-lamp, and also cheaper in power consumption, all very important things nowadays.

On top of this it produces that wonderful glareless, shadowless and evenly diffused light so essential for the preservation of eyesight.

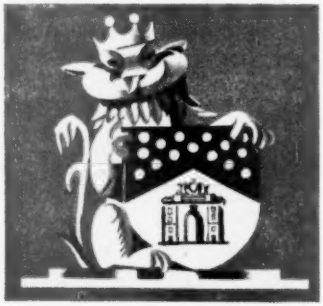
The accompanying illustration of the "Barnes" Lecture Hall of the Royal Society of Medicine is an excellent example of our lighting. The Hall is 2,250 square feet in area and 18 feet high, yet we have given this perfect indirect lighting with only 10 fittings and a power consumption of less than 1 watt per square foot.

THE "BARNES" HALL, ROYAL SOCIETY OF MEDICINE

Among other well-known users of the G.V.D. SYSTEM may be mentioned: The British Institute of Radiology; The Institute of Cardiology; St. Mary's Hospital, Praed Street; The Paddington General Hospital; St. Charles's Hospital; The Nelson Hospital; The Walsall Hospital; The Lennox Castle Hospital; and innumerable doctors, surgeons and dentists, who have installed it in their surgeries and consulting rooms and also in their homes; it is, of course, magnificent for every part of the home.

For further particulars, please apply to:

G.V.D. ILLUMINATORS 29b TORRINGTON SQUARE, LONDON, W.C.1
Telephone : MUSeum 1857



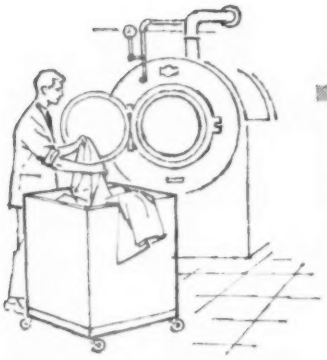
Make the most of your Bank account

Consult the National Provincial Bank about . . . *Banker's references; Borrowing; Business and personal travel facilities; Deposit (Savings) Accounts; Executorship and Trustee business; Hire Purchase; Investment; Overseas business* . . . and any other financial matters.

The full services of National Provincial Bank are available to all customers and any charges are extremely modest.
You are invited to have a word with the local Branch Manager who will be glad to give you the benefit of his knowledge and experience.

National Provincial
for friendly service
NATIONAL PROVINCIAL BANK LIMITED

Send today



FOR A FREE TESTING SAMPLE OF

HYTOX

NEW DETERGENT / STERILIZER

Hytox is a blend of non-ionic detergents and cationic bactericides.

The special properties of Hytox—outstanding cleaning power plus excellent germicidal effect—promise complete satisfaction of the most stringent needs of hygiene.

Hytox is safe for all surfaces and textiles, effective in the hardest water and extremely economical in use. Write **today** for a free sample and test Hytox yourself.

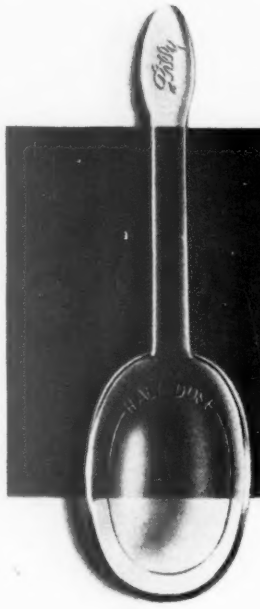
DOMESTOS LIMITED · NEWCASTLE UPON TYNE, 6

Introducing

'ILOSONE'*

LAURYL SULPHATE

SUSPENSION



A more effective treatment for common bacterial infections in children

'Ilosone' brand propionyl erythromycin ester gives quicker, higher and longer-lasting blood levels than the older erythromycin preparations. It is available as the lauryl sulphate salt, in a readily acceptable suspension. Each 5cc. contains the equivalent of 125mg. erythromycin base.

The dose is a half to two teaspoonfuls every six hours (four times daily) depending on age. 'Ilosone' Lauryl Sulphate 125 for Oral Suspension is supplied in bottles to make 60cc., each with a 5cc. plastic spoon.

* TRADE MARK

Lilly

ELI LILLY AND COMPANY LIMITED · BASINGSTOKE · ENGLAND

Proceedings of the Royal Society of Medicine

Vol. 53
151

Section of Otology

President—RONALD MACBETH, D.M., F.R.C.S.

Meeting
November 6, 1959

Some Thoughts on the Eustachian Tube

PRESIDENT'S ADDRESS

By RONALD MACBETH, D.M., F.R.C.S.
Oxford

Introductory

Although Presidential Addresses on the eustachian tube were given to the Section of Otology by Tweedie in 1931 and by Nielson as recently as 1950, I believe this to be a subject once more worthy of review.

The assessment of all varieties of deafness in the consulting room and the successful achievement of every operation designed to improve hearing, including those for congenital malformation, demand atmospheric pressure in the middle-ear cavity. In other words it behoves us as otologists never to allow the eustachian tube to be far from our thoughts.

Historical

It is clear that the ancients were acquainted with the pharyngotympanic tube. Scott Stevenson and Guthrie (1949) say that an oblique reference is made to it in an ancient Egyptian papyrus, but to Alcmæon of Sparta about 500 B.C. appears to go the honour of first describing it. Aristotle more than a century later comments upon Alcmæon's description and notes this author's belief that goats breathe through their ears as well as through their noses.

From that time anatomy suffered a dark age which lasted nearly 1,000 years and the structures of the ear were not explored and understood until the great Italian anatomists of the sixteenth century broke out of the bondage imposed by the Church. Of these Bartolomaeo Eustachio who held the Chair of Anatomy at Rome, was the first to give a clear description of the tube which now bears his name. Although he described the tube in 1563 in his "Epistola de Auditus Organis", curiously enough a picture of it does not appear in his "Tabulæ Anatomicæ". For reasons which are not clear, but which may have something to do with Papal objections, this major work was not published in Eustachio's lifetime and only came to light nearly two hundred years later in the Vatican Library.

Meanwhile, Vesalius also knew about the tube. He was Professor of Anatomy in the independent and sovereign republic of Padua, and in that enlightened City State had no scruples about publishing his knowledge.

One of his illustrious successors, Julio Casserio of Piacenza (known in Latin as Placentinus) published his work "De Vocis Auditusque" in 1600. The main part of this book is on the anatomy of the larynx of humans and of all kinds of animals. The ear appears as an addendum but it is interesting to note that Casserio must have realized that the only object of voice is that the sounds made shall be heard, and his is probably the first textual linkage of the two ends of our specialty. The illustrations in his book show the tube, but he labels it "Locus Musculi Interni" or, as we might say, place of tensor tympani. He says:

> "The meatus from the ear direct to the palate is of manifold use. First, and I think this to be the chief, because the external air transudes from the mouth to the ear, so that the implanted air which is perpetually being absorbed by the force of internal heat and so is lost, shall be conserved by renewal. The air appears in the ear partly by pulsation and partly by its own force. The second use is to carry sound from the mouth to the ear. The third is that by the use of mastications the ear is conveniently evacuated by this route of useless superfluities and that which is irritating it."

Harvey, the Englishman, went to Padua and studied under Casserio. A friend of his was Nathaniel Highmore, Fellow of Trinity College, Oxford, and a Doctor in the University, whose "Corporis Humani Disquisitio Anatomica" was published in 1651. In this book, after describing the external auditory meatus he says "The other duct in truth stretches into a common ending with palate and nostrils, designed so that the more heavy excrements of the brain and ear, which cannot get out through the tympanum, are extruded on to the palate".

The first book on anatomy to be published in

English rather than Latin would appear to be that in 1698 by William Cowper, the London surgeon. The value of his book is marred by the fact that the majority of his pictures were plagiarized from the work in Latin by the Dutch anatomist, Camper. Nevertheless, it would seem that much of the text is his own. He talks about the drum as the "tympanum of Eustachius", describes the membrane and continues "The cavity is lined with a transparent membrane which (I am apt to think) is also extended on to the Malleus, Incus, Os Orbiculare and Stapes". In discussing the tube he has this to say: "Nor could any tremulous motions be imprest on the Membrana Tympani by the External Air, if that cavity of the tympanum itself had no aperture by which its contained air could fluctuate, no more than a drum itself would sound if there were no holes in its sides. For this reason a passage from the palate to the Tympanum is formed."

The next historic figure to be mentioned is Valsalva, who was Professor of Anatomy at Bologna and whose "De Aure Humana" was published in 1704. Not only did he do Eustachio the honour of naming the tube after him, but he established its function clearly and described the method for overcoming its blockage which bears his name to-day. He conceived the bony tube to be separate from the soft tube, and not genuinely a continuation of it.

As Scott Stevenson and Guthrie relate, the eustachian catheter was devised in 1724 by a French post-master called Guyot for the relief of his own deafness. He passed it via the mouth and upwards behind his soft palate and he syringed water up it. Cleland, a Scottish surgeon, improved upon this primitive weapon in 1741; he demonstrated that it could be passed via the nostril, and connected it up by means of the excised ureter of a sheep to a syringe with an ivory end.

Adam Politzer was born in Hungary in 1835, and after an unusually cosmopolitan training became Professor of Otology in Vienna in 1861. Although we are apt to think of him in relation to his special method of air pressure adjustment, he was far from scorning the use of the catheter in difficult cases; but he evidently felt that its passage was unpleasant to the patient and not without danger to near-by structures. He used a variety of pieces of apparatus, including a pressure pump which is illustrated in the English translation of his textbook (1883). This was connected up to the catheter, and although evidently happy about its use in his own hands, he relates in his textbook that Turnbull in England had had 2 cases of unexplained sudden death following its use. It seems probable that these patients died of air embolism.

He did more than anyone to establish the doctrine that the tube has a soft section and a bony section, and he recognized that the cartilaginous wall is an incomplete ring. He noted that strictures could form, and he taught the passing of bougies via the catheter. He also made the very acute observation that where the eustachian tube is closed by reason of inflammatory swelling, the air is rarefied in the tympanic cavity, and so a condition is set up which is favourable to the exudation of fluid from the blood and lymph vessels into the tympanic cavity. He approved of the term "hydrops ex vacuo" for this condition, and thereby unwittingly provided a ready-made explanation not only for otitis media in general, but for the special aero-otitis of our day.

Politzer died in 1917 and his life therefore overlapped those of many living otologists. The very senior may well have met him.

Anatomy and Physiology

Nothing is to be gained by repeating in detail the commonly accepted gross descriptive anatomy of the pharyngotympanic or eustachian tube. This is to be found in all the standard textbooks of anatomy and otology and they differ very little among themselves. One of the most recent pictures of the tube is that given by Truex and Kellner, but the most comprehensive recent review of the anatomy has been that by Graves and Edwards in 1944. An important point calling for comment at this stage is the fact that the tensor tympani muscle originates in the dorsum of the tube in the mammalian type. Also, the proximity of the mandibular nerve to the tube is seldom realized: this is of importance in relation to the pain occurring in cases of carcinoma of the tube. Tweedie's Address stressed the importance of the tube from the point of view of sepsis. He called it the guard of the middle ear, thus underlining the current belief that its closure protected the middle ear from infection.

Nielson said "The essential function of the tube is the equalization of air pressure on the two sides of the tympanic membrane". This conception is fundamental and no attempt will be made to challenge it. But there has been a classical controversy as to whether the tube is normally shut or whether it only becomes so when air has been absorbed in the tympanum. Nielson drew the analogy between the elastic tube and the inner tube of a deflated bicycle tyre, which is kept shut by light atmospheric pressure from without, but this does not explain why

closure appears to occur immediately after pressure has been balanced. Stacey Guild came to the rescue in 1955 by examining in cross-section a series of tubes from the Johns Hopkins collection. He found that the submucosa of the soft tube contains a striking amount of elastic tissue just where it would most be needed, i.e. over the cartilaginous "cap" and along the lateral membranous wall. He concludes that this forms an elastic opponent to the pull of the muscles which open the tube, and in that sense keeps it actively shut. He found that this tissue is less developed in children and concluded that in them closure is less completely maintained, and therefore, that infection is more likely to ascend the tubal lumen.

In 1940 McMyn made the suggestion that a thin film of mucus may help to "gum" the walls together while at rest, and he gave a detailed account of the muscles of the palate. He concluded that the tensor palati is virtually the only muscle concerned in opening the tube, and that this muscle acts upon the membranous lateral wall of the tube, while the medial cartilaginous wall moves very little.

The idea that the tensor palati is of prime importance receives striking support from the situation in the whales and porpoises where this muscle is very well developed in spite of the fact that these animals have no soft palate.

It is a matter of common experience that the ear "clicks" with every movement of swallowing, yawning or hiccup, and clinical confirmation that this muscle indeed does cause the opening of the tube and produce the click is found in cases of palatal myoclonus. The 3 cases reported by Chadwick and Macbeth exemplified this. In each of them an irregular "click" could be heard by the observer and in one of them movement in the neighbourhood of the pharyngeal orifice could sometimes be seen.

Graves and Edwards state that the normal adult swallows once per minute on an average when awake and once every five minutes when asleep, while in sucklings the rate is five times per minute awake and three times asleep. This automatic action is normally extremely efficient and quite unconsciously achieved.

Quite different evidence comes from those rare patients whose tubes are permanently open. These complain of a blowing noise heard with every breath, and a humming tinnitus, but they have no "clicks". They are relieved by applying a mild irritant to the mouth of the eustachian tube. This causes local swelling and the "click" returns.

It is pertinent to enquire what effect this musculo-elastic mechanism might have upon the occurrence of otitis media on the one hand and its resolution on the other. Does opening or closure encourage ascending infection? Clearly the efficient opening of the soft tube must aid drainage, and an older generation was in the habit of encouraging patients with earache to suck sweets or even to chew gum. Children, we know, have otitis media more often than adults, and their eustachian tubes are relatively wider and absolutely shorter. It has, therefore, been argued that the more frequent and complete opening of the tube in children actually encourages the ingress of infection. Certainly if infants are bottle-fed lying down they tend to develop otitis media, and probably there is direct but descending infection in this situation. But sucklings actually are freer from otitis media than children in older age groups. Surely we must believe that their almost incessant swallowing movements do in fact help to keep them clear. In older children, the hypertrophy of lymphoid tissue in the nasopharynx provides a new factor which completely alters the efficiency of this mechanism, so that the tube remains unnaturally shut.

It is well known also that cleft-palate patients tend to suffer from otitis media. It has often been assumed that this is because the eustachian tube is in some way unprotected and therefore that infection readily ascends its lumen. This would seem to be most unlikely, since the ciliary action is powerfully in the opposite direction, but I should like to suggest that in cleft palates the two tensor palati muscles have nothing against which to pull, and in consequence the tube tends to remain closed. Infected material from the pharynx readily passes into the lymphatics of the tube and is drawn into its lumen and that of the middle ear because of the relative negative pressure existing there.

The conclusion seems inescapable that the tube is kept clear by a combination of ciliary action and rhythmical opening, and that so far from being a protective mechanism, closure of the tube actually favours the development of otitis media. We are in fact back to Politzer.

Clouding our mental picture of what goes on in the eustachian tube in conditions of normality and disease is ignorance of the part played by the rigid-walled bony section and its junction with the elastic tube which anatomists call the isthmus. It is not unnatural to assume that obstruction should occur at the isthmus, and no doubt this has taken place in gross chronic middle-ear infection and particularly in those cases of syphilis and tuberculous disease so commonly met in Europe in Politzer's day. But Rees-Jones and MacGibbon injected radiopaque material into the eustachian tubes of aviators suffering from tubal obstruction due to altitude changes, and found on radiographic examination that the majority showed a block in the elastic portion of

the tube. Others have subsequently noted the same thing.

In 1944 Schwartzbart put forward the idea that the bony tube is in reality nothing but the narrowed antero-inferior portion of the tympanic cavity. He said that the isthmus is purely artificial and that it is brought about by the bulge of the carotid canal on the one hand and the origin of the tensor tympani muscle on the other.

Schwartzbart suggested that we should restrict the term eustachian tube to the elastic section, that we should call the bony tube the protympanum and that we should include our present hypotympanum and the protympanum in a new term, the bitympanum. Common-sense anatomical and physiological considerations would support this conception, the bony box being concerned with sound transmission and the elastic tube with equalization of air pressures under the action of the tensor palati.

Embryology

The literature on the embryology is confusing. The eustachian tube develops from the tubotympanic recess, an outgrowth of the primitive pharynx. Most writers have followed Frazer in saying that this recess develops from the first branchial pouch, and the middle-ear cavity possibly from the second pouch. That the external auditory meatus arises from the first branchial groove and grows to meet the outgrowing tube seems undoubted and the loose gelatinous cellular tissue into which these two tubal structures grow probably gives rise to the temporal bone, tympanic membrane, and ossicles.

Bast and Anson say that the tubotympanic recess reaches the area of the middle ear by about the end of the second month of fœtal life. They note that there is some question as to whether it closes up during the third month and reappears a little later, but are of the opinion that it does not do this. Nevertheless such a closure and reopening is an important possibility, as will be noted later when consideration is given to the evidence of comparative anatomy.

The various authors are not clear about whether the lining of the tympanum, the epitympanum and air cells is derived from an invasion by the epithelium of the developing tubo-tympanic recess, or whether it originates *de novo* in the jelly-like mass which represents the middle and internal ears. Schwartzbart noted that the lining in fact develops at just about the same time in fœtal life as the endothelium of the blood vessels is formed elsewhere, and he believed that we should regard this basically as an endothelial or serous rather than a mucous membrane. If the bony tube be regarded as part of the middle ear it is easier for us to understand the occurrence of the air cells which are found connected with it.

Comparative Anatomy

Thoughts about the embryology of a part should lead one to the comparative anatomy, for much that is obscure or irrational in the one can often be explained by the other. This region is no exception, but those who would delve into its comparative anatomy should be warned that in so doing they will find themselves deeply involved in a major controversy which has vexed zoologists for a number of years. Briefly the question is whether the middle ears of reptiles and of mammals are homologous. From among ourselves, Tumarkin would appear to be the only bold adventurer in this domain and he deserves much credit for breaking a lance on behalf of otology.

The zoological controversy has been admirably summarized by Shute of the Anatomy Department at Cambridge and he has put up a theory of his own which seems to resolve many of the difficulties.

As far back as 1913 Gaupp pointed out that the eardrum of reptiles lies above the mandible, while that of mammals is submandibular. Among the anatomical differences which followed from this essential feature were:

(1) That whereas the adductor mandibuli internus muscle of reptiles is ventral, its mammalian homologue, the tensor tympani, has become dorsal.

(2) The eustachian tube has a narrow character and an upward and backward inclination in mammals as compared with the horizontal and widely open position in reptiles such as lizards (Figs. 1 and 2).

(3) The internal carotid artery changes its position from dorsal to ventromedial in relation to the middle ear and tube.

On this basis Gaupp claimed that the mammalian form of middle ear was not homologous with the reptilian and that it must have evolved separately. An obvious difficulty about accepting this idea is the anatomical similarity between structures of similar function, especially the stapes, in the two groups.

The chief protagonist of the opposite view has been Goodrich, who thought that the eustachian tube and middle ear of reptiles and mammals were entirely homologous, and he overcame the argument based upon the changed anatomy by explaining that the tympanic membrane had migrated downwards so that it came to lie at a lower position on the body surface. This obviously introduced a major difficulty not only in relation to the conception of just how this

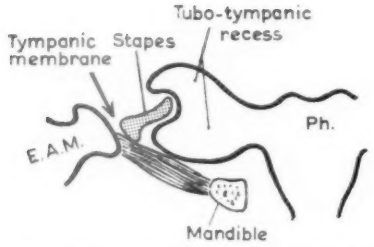


FIG. 1.—Illustrates basic reptilian type of middle-ear apparatus. Single ossicle, wide pharyngo-tympanic tube. Adductor mandibuli internus muscle (= tensor tympani) lies ventral to tube. Figs. 1–4 modified after Shute.

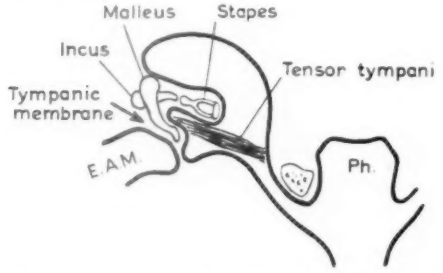


FIG. 2.—Illustrates basic mammalian type of middle-ear apparatus. Ossicles are multiple and tensor tympani is dorsal to narrow tube.

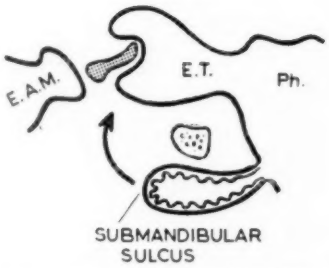


FIG. 3.—Illustrates middle ear of lacertid lizard. Submandibular sulcus and wide pharyngo-tympanic tube both present.

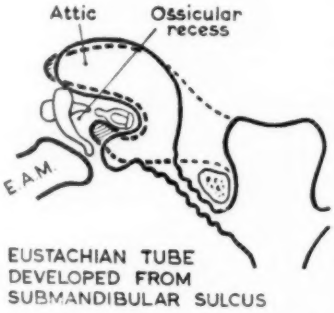


FIG. 4.—Illustrates Shute's suggestion of how the narrow mammalian tube may have developed from the submandibular sulcus of reptilian types and replaced the wide tube (shown as a dotted line). Potential epithelial rests are shown in attic and in neighbourhood of stapes.

happened, but also because the only intermediate types available for study were fossil remains.

Tumarkin has given some support to Gaupp's general idea, and has based his argument upon considerations of function obtaining in the mammal and those obtaining in the amphibia and reptiles. He has noted, for example, the very large size of the stapes and its articulation with the mandible in some prehistoric reptilians and has argued that it could not be utilized as a moving part in a sound conducting vehicle. Some of the zoologists have come back quickly with the retort that perhaps these beasts needed only to be aware of the vibrations produced by the footfalls of one another, and that such vibrations might indeed have activated such a stapes. As Shute points out, however, in assessing the hearing needs of animals we should not assume that something like a human ear is necessary.

Westoll tried to resolve the difficulty in 1943 by suggesting that in mammals a new diverticulum grew out from the middle ear, or possibly from the pharynx. He actively developed the idea of a new offshoot from the middle ear, but the weak point obviously is that it does not account for the new position of the eustachian tube in relation to the pharynx itself.

In 1956 Shute put forward his own theory which aimed at retaining the idea of homology, but explained the new position of what we to-day call the middle-ear cleft. He pointed out that the mammalian embryo goes through a phase where its tubo-tympanic recess is rather similar to the eustachian tube of reptiles. He also found that in lacertid lizards there is developed in the lateral wall of the pharynx a well-marked diverticulum called the submandibular sulcus, which grows outwards below the existing eustachian tube and below the level of the mandible (Fig. 3). The function of this sulcus in the lizard is thought to be to facilitate distension of the pharynx and to aid in the excretion of carbon dioxide. The development of a thorax in later types would render this function obsolete. Meanwhile a more complicated and exact type of hearing organ was needed by the mammals, involving a middle-ear cleft normally shut, but capable of opening, and the sulcus was ready at hand to provide a new eustachian tube.

Shute's idea is that the sulcus grew into and

fused with the middle ear, the cochlea became a much more obvious organ and the old pre-mammalian tube disappeared (Fig. 4). He agrees that there is a missing embryological link in the chain of proof, but the remark by Bast and Anson that possibly the human tube disappears in the third month to reappear a little later is now seen to be important if true. If we accept the essentials of Shute's argument, other anatomical details fall into place. In a recent personal communication Shute has also said that very likely the auditory apparatus, being a late evolutionary need, does not originate from the branchial structures at all; perhaps, therefore, we are being needlessly hide-bound in holding on to that idea.

Assuming that in fact a pre-mammalian type of eustachian tube was produced at one stage in the human embryo, later to be pushed out of existence and replaced by a new tube, it seems that we have here a possible explanation for the occurrence of epithelial rests in the middle ear, and therefore of one form of cholesteatosis. In my experience cholesteatosis is very nearly as commonly found around the incudo-stapedial joint and the footplate of the stapes as it is in the attic, and these nooks or crannies might be just the places where replacement of one embryological epithelial layer by another might be incomplete. Again my experience is that cholesteatosis occurs almost as commonly in cellular mastoids as in sclerotic, and quite often in young children. It is by no means a new idea that some cases of middle-ear cholesteatosis are of congenital origin and this would have a ready explanation on a basis of Shute's theory. The argument continues; but quite clearly further work is needed on the embryology of the terrestrial mammalian ear.

Histology

Unfortunately, neither accepted embryology, nor Schwartzbart's conception that the bony tube is really hypotympanum nor Shute's theory gives a completely satisfactory explanation of the essential differences between the tubal mucosa and the epithelial lining of the middle ear proper with its cellular extensions. These differences are marked. In some animals the point of demarcation is abrupt, but in human specimens the point of change from the columnar ciliated mucosal epithelium of the soft tube to the flattened cuboidal type of the middle ear is gradual and variable. It would appear that at birth the junction point is fairly constantly found near the attachment of the soft tube but that later there is a migration of the true mucosal elements into the middle ear proper. Schwartzbart feels that we should regard the occurrence of true mucosa in middle ear and mastoid antrum as a reaction to infection and he makes the point that soft tissue layers are not so fixed anatomically as are skeletal tissues.

The question of the presence or absence of lymph tissue in the tubal wall has been a matter for doubt. Various earlier writers noted lymphoid tissue in the wall of the soft tube, notably Gerlach in 1875. Others have followed his lead and the term "Gerlach's tonsil" has crept into the literature. This conjures up a definite anatomical entity of regular occurrence, whereas the writers in question almost without exception were describing findings in post-mortem specimens taken from sufferers from infections of the naso-pharynx and middle ear. However, it became accepted teaching that middle-ear deafness of tubal origin was often due basically to continued swelling of lymphoid tissue which was within the tube, and thus out of reach of traditional surgery.

The matter assumed a new importance in the Second World War in relation to the hearing of airmen and in particular with the development of so-called aero-otitis. The Baltimore school were in the lead in insisting upon the presence of this lymph tissue, and they pioneered in the treatment by irradiation of eustachian deafness supposedly due to this cause. Curiously enough, however, they gave no account of having examined the Johns Hopkins collection of microscopical material in support of their claim.

Graves and Edwards thought there was a collection of subepithelial tissue in the mucosa of the tube.

Fowler of New York in a series of articles has described lymphoid tissue in the mucosa of the tube. His material was largely taken from U.S. airmen killed while flying, and in point of fact he stressed the essential similarity between these cases of eustachian salpingitis and the chronic infection of bronchi and nasal sinuses. In both classes of case there were varying degrees of subepithelial collections of migratory round cells. His control material from ground staff showed "nothing like that".

The most recent work on the subject is by Aschan of Uppsala in 1954. He reviewed the previous literature, noted that there was a good deal of reputable evidence against an anatomical lymphoid collection, and thought that the opposite idea was based upon unsure premises. He gave an account of microscopic sections of the eustachian tube from 10 human fœtuses and 39 human subjects of all ages. As a result of this investigation he concluded that "Histological examination on no occasion suggested that the lymphatic tissue of the nasopharynx extends to,

still less involves, the pharynx at the orifice of the eustachian tube". He stressed that the term oto-salpingitis should be used in relation to eustachian deafness.

If Aschan is correct in his view (and there is good reason to believe that he is) it is clearly incumbent upon us to cease to teach the tubal tonsil story. Also it is necessary drastically to overhaul the current conception of what is being done when the eustachian tube is irradiated for stubborn deafness of eustachian type. This question has been posed to two well-known radiotherapists and they both have replied that they had assumed they were treating hypertrophic lymphoid tissue. It appeared that their basis for this assumption was that otologists had told them that this was the case. They both agreed, however, to continue to give a treatment which they regarded as demonstrably valuable.

Further Tubes Examined

A few dissections have been made of the eustachian tube in human and animal specimens, and Dr. Hugh Cowdell, Department of Pathology, Radcliffe Infirmary, has kindly prepared photographs and photomicrographs.

(*a*) *The human material* consisted of a newborn and premature fœtus, a suckling of a few weeks old, a child of 6 years and a teenager. The last 3 had died of conditions which, it was thought, would not have produced immediate pathology in the eustachian tube, though terminal otitis could not be excluded as a clinical possibility. Dr. Cowdell sectioned these 4 and 4 additional human specimens. At dissection the main point seemed to me to be that the bony tube is part of the middle ear (Fig. 5).

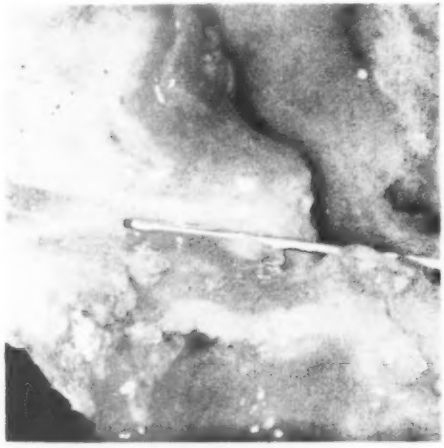


FIG. 5.—Shows the right eustachian tube of a 5-week-old infant. Head of probe lies in protympanum (bony tube). It will be noticed how this is merely a funnel-shaped prolongation of the middle-ear cavity. ×5.

Microscopically the main findings to note were:

(1) That the so-called bony tube is inconstant in form. Although the bony wall may project from the skull base at one point or more, it may be almost missing at others.

(2) That anatomical lymphoid aggregations do indeed stop short of the pharyngeal end of the tube.

(3) That irregular aggregations of round cells are to be found in the submucosa of the tube and these are more evident in older children and the young adult.

(4) That the columnar ciliated epithelium, with its goblet cells and mucous glands, enters the bony tube and seems to stop there in the few specimens examined.

(5) That the character of the epithelium lining the middle ear and cells is much more like a serous membrane than a mucous membrane. Mucous glands are not a regular constituent (Figs. 6, 7 and 8).

An interesting finding in one of the specimens has been a deep fossa of Rosenmuller full of anatomical lymphoid follicles. The appearance suggests that this fossa might have been mistaken for the tube on previous occasions, thus leading to the story that the tube contained lymphoid tissue (Fig. 9).

(*b*) *The animal material* consisted of a young sheep, the slide of a cat's middle ear and tube lent by the University Department of Histology, and a porpoise provided by Dr. F. C. Fraser of the South Kensington Museum.

At dissection *the sheep* showed few features differing from the human except that the bony tube or protympanum was relatively longer. Under the microscope the chief points to notice were that, as in the human, there were no anatomical lymphoid aggregations, although there was some evidence of infection in the specimen examined and in consequence there was round cell infiltration near the pharyngeal end of the tube. The change from ciliated columnar epithelium to flattened occurred, as in the human, on the bone of the protympanum. There was some evidence of the commencement of a diverticulum in the soft tube.

The cat showed an abrupt change in the character of the mucous membrane from pseudo-stratified ciliated to flattened cubical at the point of change from soft to bony tube. There was no anatomical lymphoid deposit. Again

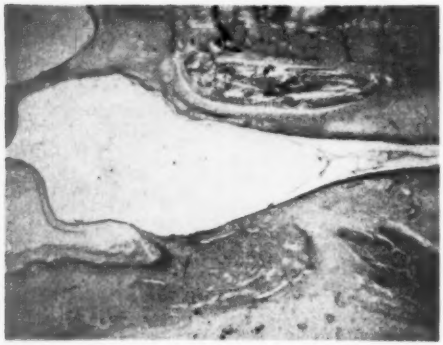


FIG. 6.—Section through the specimen shown in Fig. 5. The columnar epithelium gives place to a thin flattened type at the protympanic level. ×8.

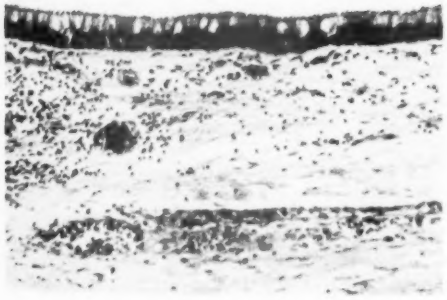


FIG. 8.—High-power section through eustachian tube of a patient aged 20, near the pharyngeal end. Although the patient died of head injury the tube shows dense round cell infiltration in response to an inflammatory process. There are no true lymphoid aggregations. ×96.

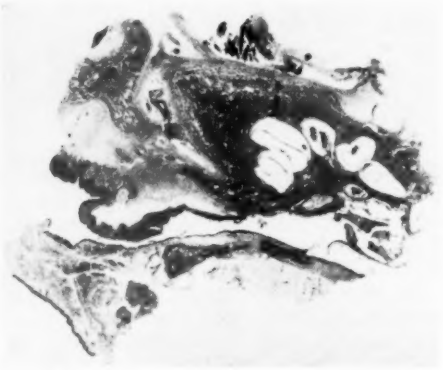


FIG. 7.—Section through the entire tube and middle ear of a 5-week-old infant. The obliquity of the walls of the so-called bony tube will be noted. Mucous glands are numerous at the pharyngeal end, but there are no lymphoid follicles within the tube. There is an abrupt change from columnar to flattened epithelium at entrance of middle ear proper. ×2.

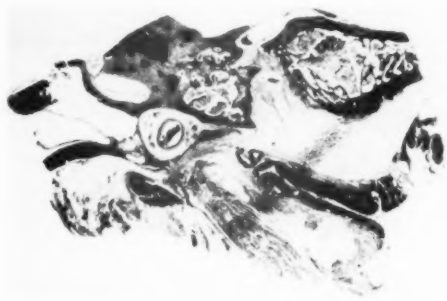


FIG. 9.—Section from the same patient as in Fig. 8, showing a deep fossa of Rosenmuller lined with lymphoid tissue. Such a finding might have been mistaken for the eustachian tube, and thus given rise to the impression that "Gerlach's tonsil" is an entity. ×1·3.

there was the suspicion of a small diverticulum.

The porpoise.—The condition in the porpoise was interesting. On theoretical grounds it had seemed likely that there might be some kind of valves in the tube, so that the animal could increase the air pressure in its middle ear on diving, and so that air should not escape. Personal consultation with Fraser and Purves at the Natural History Museum, South Kensington, revealed that such valves do indeed exist in cetaceans but that they are ancillary to a more complicated and efficient mechanism. It must be remembered that these are highly evolved mammals, which have forsaken the land and returned to the sea. Fraser and Purves (1959) have shown that in them the periotic bone has largely disappeared, leaving a soft connective tissue mass, while the venous sinus system of the area has remained and hypertrophied. In addition a highly complex series of air sacs has developed from the middle ear and tube (presumably the homologues of the air cells of man) and these have pushed their way into the vascular mass. In addition the sacs are filled with a foam containing mucus and oil in watery suspension. This enables the ossicular system to remain effectively in contact with air and minimizes air loss (Fig. 10).

On diving the pressure on the tympanum is increased from without, while the pressure in the middle-ear and air-sac spaces remains at approxi-

FIG. 10.—Vertical slice through the eustachian tube of a porpoise. Smaller probe is in pharyngeal orifice, larger in the entrance to middle ear. A large dilatation containing flap valves is seen, together with air spaces. Tensor palati muscle lies below tube and is invaded by air spaces. Tympanic bulla is shown high on left. ×0·9.

mately that of the atmosphere. This is compensated by an opening up of the venous plexus around the air spaces, which compresses them and balances the pressure. The role of the valves would appear to be to prevent escape of foam from the middle-ear system, but to allow the entry of air when the animal surfaces again. Their structure is of connective tissue with a mucosal covering and they contain no striped muscle. An unexpected finding in the slides prepared by Cowdell has been that the air sacs actually invade the muscle tissue of the tensor palati and this further emphasizes the important contribution which this muscle makes to the physiology of the tube (Figs. 11 and 12).

The net result of this arrangement in cetaceans is that they hear sounds transmitted through water by means of an accurate "air-conduction" mechanism. There is some evidence that, as in bats, these animals identify objects by reflected sound, and the internal ear is protected from massive non-directional "bone-conduction" stimuli by being surrounded by thick ivory bone which in its turn is suspended in a spongy air-sac system. The point to make here, however, is the importance of the tube as part of an accurate system for the identification and localization of sound.

The guttural pouch of the horse.—This is a saccular diverticulum of the eustachian tube. It is filled with air and is lined with mucous membrane. It would seem to be homologous with the small diverticula noted in sheep and cat, but it is doubtful if it is so with the air sacs of the porpoise. A textbook of veterinary anatomy states that its function is quite unknown, but that it is commonly the site of infection.

FIG. 11.—Low-powered section of the valves showing how the air spaces actually invade the muscle. ×1.

FIG. 12.—High-power magnification of the valves. ×8.

Clinical Problems

(*a*) *The failed inflation.*—Politzer's method of inflation has its main application in children. Like Valsalva's it has the disadvantage of acting upon both tubes at once, and more particularly upon the tube which is possibly not at fault. Furthermore, its action is achieved so rapidly if at all that the observer can gain no information through an auscultation tube of the kind of noise which accompanies inflation. So it would seem that the catheter is the correct instrument to use in adults if one wishes to judge of the reasons for a eustachian block, and particularly if one wishes to combine inflation with myringotomy. Its discomfort is minimal after surface anæsthesia, which should always be used.

But from time to time one fails to cause an entry of the air altogether. Sometimes this is because of an anatomical obstruction in the nose, in which case it is usually simple to pass the catheter through the opposite nostril. Sometimes, however, the end of the catheter is lying impeccably in the tube but no air passes. Here the walls of the soft tube may be so swollen that the force available is not sufficient, as is the case in aero-otitis; or possibly there may be a really viscid plug of mucus blocking the tube. Negus drew attention to this possibility when discussing Neilson's Address in 1950 and noted the analogy with the plug propelled into the mouth of a bronchus by ciliary action in lung collapse.

It is suggested that these are just the cases in which the passage of a gum-elastic bougie is helpful. This is a valuable little instrument, whose use has undeservedly fallen out of favour.

But we are sometimes left with the case which still will not be inflated. Often if that patient be sent away and given steam inhalations success attends one's efforts a week later; but if failure continues, a myringotomy and inflation downwards through Siegle's speculum may be tried. This too may fail. It would then seem reasonable that our command of modern techniques permits us to explore the patient's middle-ear cavity through a Rosen's type of incision; any fluid found can be evacuated and exploration can be combined with a renewed attempt at inflation from below with "the lid off the tube".

As an example may be quoted the case of R. D., a busy farmer, aged 50. Here inflation and myringotomy repeated at intervals over a period of four months failed to overcome his otosalpingitis and eustachian block. Exploration of the tympanic cavity showed only œdematous mucosa, but the operation was succeeded by a spontaneous opening of the tube two days later and a restoration of the patient's hearing.

(*b*) *The chronic inflatee.*—This patient is well known to most otologists. She is usually elderly, often with unrelieved otosclerosis, and has a rooted antipathy to hearing aids. She has been in the habit of visiting Mr. So-and-so at regular intervals and will we please take her on? She is convinced that she is given relief by her visits—in spite of the contrary evidence of hearing tests—and in particular that her hearing is being prevented from worsening. Perhaps we do her some good at psychogenic level, but since aids have become less unfashionable she is becoming a rarer customer.

(*c*) *Post-operative inflation.*—It should be impertinent to mention that it must be remembered that a foot-plate operation or tympanoplasty may appear to have failed solely because the tube has not opened up post-operatively. It is in fact very easy to forget this, and judicious inflation after two or three weeks may be spectacular in its effect.

(*d*) *No tube present.*—Politzer reported that in congenital defects the eustachian tube may be absent, and others have noted this since. This is so in some cases of the Treacher-Collins syndrome. Present techniques have not yet reached the point where in the absence of a eustachian tube it is possible to arrange that the round window is in a closed air-containing and pressure-balanced cavity, and the best which can be done is to make it communicate with the outside world in the same phase as the oval window. Reconstructive surgery is therefore less likely to give a good hearing improvement than in cases where a tube is present.

(*e*) *Secretory otitis.*—This is essentially an oto-salpingitis. The patient is usually an adult, often in the older age group, whose middle ear fills up with thin fluid, which one can expel in the form of a froth after inflation and myringotomy. These people may be exceedingly difficult to cure. Their mastoid air cells may also be full of this fluid, but a cortical operation is often useless. A knowledge of the anatomy of the tube may give very little information about the ætiology of this condition, but surely a realization that the peritubal cells are part of the tympanomastoid system gives a clue to the persistence of the disease after a cortical operation.

(*f*) *Carcinoma of the eustachian tube* sometimes masquerades in its early stages as secretory otitis. The diagnosis may be suspected if the fluid in the middle ear is blood-stained, and when fifth nerve pain occurs it should be confirmed. In these cases a biopsy from the post-nasal space is unlikely to be positive in the early stages, but Dr. Frank Ellis's technique of drill biopsy done through the nostril and going deeply into the peritubal area may give a positive result and so enable one to avoid a transpalatal exploration.

My colleague, Mr. Gavin Livingstone, has kindly given me the opportunity of seeing two such cases and they are mentioned here with his permission.

A cytological examination of the tubal fluid might also yield a positive result but I have no knowledge of the use of the technique in this connexion.

(*g*) *Skin-diving.*—The new sport of diving to considerable depths while wearing nothing more protective than an oxygen mask has provided problems for the otologist similar to those offered by aviation, though the temperature of our coastal waters makes it unlikely that many cases will come to the British otologist. Fields has surveyed the subject. He points out that as the diver goes deeper he develops "face-squeeze" because of the water-pressure upon his mask. The mouth and nasopharynx are open and therefore the pressure within the mask is relatively lowered. Earache comes on, but in the early stages the tube can be cleared by means of Valsalva's manœuvre. The next stage is very like aero-otitis in which turgescence leads to an impermeable block and ultimately to effusion.

(*h*) *Teeth and the eustachian tube.*—It is elementary to think of the teeth in relation with pain referred to the ear, but it is doubtful if they are often associated in our minds with tubal difficulties. Young in quite another context has, however, demonstrated a lymphatic connexion between the teeth and the eustachian tube in monkeys.

It is possible that the earache of teething infants is often due to a minor otitis media. The pink drumhead occurs too often to be ignored, and this may mean an otosalpingitis of lymph-borne origin.

Allied to this condition is the case of the adult patient with periodontal sepsis who comes complaining of deafness. This turns out to be of conductive type, and extraction of the offending teeth cures the deafness.

Another unusual type of eustachian deafness has been described by Brewer. He states that the overclosed jaw of the edentulous patient allows the belly of the tensor tympani to become slack, and so to block the tube. I have not met this condition, but it is mentioned for completeness.

Conclusion

In the adult human the eustachian tube measures $1\frac{1}{8}$ to $1\frac{1}{2}$ in. (31–38 mm) and one would have thought that it should be reasonably easy to learn all that there is to know about such a small and fixed structure. But it does two odd things—it runs from within a soft-tissue viscus into a cavity of the skull; and it links the two major areas of our specialty. On its brief but entertaining course it has many important companions and neighbours, and it seems unlikely that the last has been written about it.

Acknowledgments.—The author acknowledges with gratitude help and advice given particularly by Dr. Hugh Cowdell of Oxford, Dr. G. C. D. Shute of Cambridge, Dr. F. C. Fraser and Mr. P. E. Purves of the Natural History Museum, South Kensington; the Theatre Nursing Staff of the Department of Otolaryngology at Oxford; Miss A. Arnott and Miss M. McLarty, the Hospital artists.

REFERENCES

ASCHAN, G. (1954) *Acta otolaryng., Stockh.*, **44,** 295.
BAST, T. H., and ANSON, B. J. (1949) The Temporal Bone and the Ear. Springfield, Ill.
BREWER, D. W. (1958) *Arch. Otolaryng., Chicago*, **68,** 451.
CASSERIO, J. (1600) De Vocis Auditusque Organis Historia Anatomica. Ferrariae.
CHADWICK, D. L., and MACBETH, R. G. (1953) *J. Laryng.*, **67,** 301.
COWPER, W. (1698) Anatomy of the Human Bodies. Oxford.
EUSTACHIO, B. (1563) Epistola de Auditus Organis.
FIELDS, J. A. (1958) *Arch. Otolaryng., Chicago*, **68,** 531.
FOWLER, E. P. Quoted by Aschan (1954).
FRASER, F. C., and PURVES, P. E. (1959) *Endeavour*, **18,** 70, 93.
GAUPP, E. (1913) Quoted by Shute (1956).
GERLACH, J. (1875) *Mschr. Ohrenheilk*, **9,** 48.
GOODRICH, E. S. Quoted by Shute (1956).
GRAVES, G. D., and EDWARDS, L. E. (1944) *Arch. Otolaryng., Chicago*, **39,** 359.
GUILD, S. R. (1955) *Ann. Otol. Rhin. Laryng.*, **64,** 537.
HIGHMORE, N. (1651) Corporis Humani Disquisitio Anatomica. Hagæ-Comitis.
MCMYN, J. K. (1940) *J. Laryng.*, **55,** 1.
NEGUS, V. E. (1951) *J. Laryng.*, **65,** 617.
NIELSON, D. F. A. (1951) *J. Laryng.*, **65,** 614.
POLITZER, A. (1883) Textbook of Diseases of the Ear and Adjacent Organs. London.
REES-JONES, G. F., and MACGIBBON, J. E. G. (1941) *Lancet*, ii, 660.
SCHWARTZBART, A. (1944) *J. Laryng.*, **59,** 47.
SHUTE, C. C. D. (1956) *J. Anat., Lond.*, **90,** 261.
STEVENSON, R. S., and GUTHRIE, D. (1949) A History of Otolaryngology. Edinburgh.
TRUEX, R. C., and KELLNER, C. E. (1948) A Detailed Atlas of Head and Neck. New York.
TUMARKIN, I. A. (1955) *Evolution*, **9,** 221.
TWEEDIE, A. R. (1931) *Proc. R. Soc. Med.*, **24,** 1.
VALSALVA, A. M. (1704) De Aure Humana Tractatus. Utrecht.
WESTOLL, T. S. (1943) Quoted by Shute (1956).
YOUNG, M. W. (1949) *Anat. Rec.*, **103,** 524.

BOOKS RECEIVED FOR REVIEW

Abelló (J.). Biologia del cáncer. pp. 142. Madrid: Libreria Cientifico Medica Española. 1958.

Auld (P). Honour a physician. pp. 270. London: Hollis and Carter. 16s. 1959.

Brindley (G. S.). Physiology of the retina and visual pathway. pp. xi + 298. London: Arnold. 35s. 1960.

C.I.O.M.S. The biochemical response to injury. A Symposium organized by the Council for International Organizations of Medical Sciences. Edited by H. B. Stoner with the assistance of C. J. Threlfall. pp. xi + 467. Oxford: Blackwell. 57s. 6d. 1960.

Clinical Radiology. The Journal of the Faculty of Radiologists. Volume 11, No. 1. pp. xvi + 68. Edinburgh and London: Livingstone. Subscription £3 3s. per annum. 1960.

Colby (F. H.). Pyelonephritis. pp. vii + 214. Baltimore: Williams and Wilkins. London: Baillière. 60s. 1959.

Goldstein (L. A.). The surgical treatment of scoliosis. Appendix: Anæsthesia in scoliosis. By D. V. Thomas. pp. xi + 116. Springfield, Ill.: Thomas. Oxford: Blackwell. 54s. 1959.

Gould (S. E.), ed. Pathology of the heart. 2nd edit. pp. xvi + 1138. Springfield, Ill.: Thomas. Oxford: Blackwell. £13. 1960.

McKusick (V. A.). Heritable disorders of connective tissue. 2nd ed. pp. 333. St. Louis: Mosby. London: Kimpton. 90s. 1960.

Maigne (R.). Les manipulations vertébrales. pp. viii + 245. Paris: Expansion Scientifique Française. 1960.

Miller (F. J. W.), *et al.* Growing up in Newcastle upon Tyne. pp. xxi + 369. London: Oxford University Press (for the Nuffield Foundation). 25s. 1960.

Modern Treatment Yearbook, 1960. Edited by Sir C. Wakeley. pp. x + 310. London: Medical Press. 33s. 1960.

Parsons (W. H.), ed. Cancer of the breast. American Lecture Series No. 355. pp. xv + 232. Springfield, Ill.: Thomas. Oxford: Blackwell. 60s. 1959.

Pattison (F. L. M.). Toxic aliphatic fluorine compounds. pp. xi + 227. Amsterdam, London, &c.: Elsevier Publishing Co. 18s. 1959.

Pittman (D. J.), ed. Alcoholism. pp. xviii + 96. Springfield, Ill.: Thomas. Oxford: Blackwell. 30s. 1959.

Pitts (F. R.). The physiological basis of diuretic therapy. pp. xiv + 332. Springfield, Ill.: Thomas. Oxford: Blackwell. 78s. 1959.

Rank (B. K.), and **Wakefield (A. R.).** Surgery of repair as applied to hand injuries. pp. xiv + 283. Edinburgh and London: Livingstone. 45s. 1960.

Raven (R. W.), ed. Cancer. Vol. 6. pp. ix + 500 + 17. London: Butterworth. 85s. 1959.

Reed (H.). The essentials of perimetry. pp. xi + 192. London: Oxford University Press. 45s. 1960.

Rider (J. A.), and **Moeller (H. C.),** eds. Disturbances in gastrointestinal motility. pp. xiv + 387. Springfield, Ill.: Thomas. Oxford: Blackwell. £5 4s. 1959.

Salzmann (K. D.). The ætiology and arrest of pre-eclamptic toxæmia with early ambulant treatment. pp. viii + 69. London: Lewis. 10s. 6d. 1960.

Shaw (R. R.), and **Paulson (D. L.).** The treatment of bronchial neoplasms. pp. xv + 135. Springfield, Ill.: Thomas. Oxford: Blackwell. 64s. 1959.

Smillie (I. S.). Osteochondritis dissecans. Loose bodies in joints. Etiology, pathology, treatment. pp. viii + 224. Edinburgh and London: Livingstone. 60s. 1960.

Smith (C. A.). The physiology of the newborn infant. 3rd ed. pp. xii + 497. Springfield, Ill.: Thomas. Oxford: Blackwell. 95s. 1959.

Smith (E. B.), *et al.* Principles of human pathology. pp. xi + 1123. New York: Oxford University Press. 95s. 1959.

Stowens (D.). Pediatric pathology. pp. xiii + 676. London: Baillière. 160s. 1959.

Symposium. Proceedings of the first annual symposium on cinefluorography, sponsored by the Department of Radiology, University of Rochester, School of Medicine and Dentistry, Rochester, New York, November 14 and 15, 1958. Edited by G. H. S. Ramsey *et al.* pp. xvi + 266. Springfield, Ill.: Thomas. Oxford: Blackwell. 94s. 1960.

Symposium. Proceedings of a symposium on immunization in childhood, held in the Wellcome Building, London, May 4 to 6, 1959. pp. 139. Edinburgh and London: Livingstone. 17s. 6d. 1960.

Symposium. The operation of sterilizing autoclaves. A symposium held at Brighton Technical College, May 9, 1959. pp. 45. London: Pharmaceutical Press. 7s. 6d. 1959.

Adjusted Formula

for

CERUMOL

Regd. TRADE MARK

for the easy removal of ear wax

Since some sensitive individuals occasionally complain of a mild smarting in the ear when Cerumol is used, a slight adjustment has been made to the formula and base.

The efficacy of the product is unchanged but the possibility of producing any unpleasant sensation has been eliminated.

The formula is now as follows :
Active constituents per 100 ml.

p-dichlorobenzene B.P.c.	**2 G.**
Benzocaine B.P.	**2.7 G.**
Chlorbutol B.P.	**5.0 G.**
Ol. Terebinth B.P.	**10 ml.**

Pack for surgery use :- 10 ml. Vial—separate dropper included—Basic N.H.S. Cost 2/8d.

Pack for hospital use :- 2 oz. bottles.

If you would like to test this slightly adjusted formula please write or telephone us for a sample.

LABORATORIES FOR APPLIED BIOLOGY LTD.
91 Amhurst Park, London, N.16. Telephone : STAmford Hill 2252/3

PERDILATAL*

in the treatment of sudden perceptive deafness and Méniere's syndrome.

* Vascular spasm may well be responsible for the majority of these cases.**1**

* Vascular changes in the labyrinth are an important factor in the physiopathology of Ménière's disease.**2**

* In the treatment of Ménière's disease emphasis must be put upon early restoration of blood flow to the inner ear.**3**

* Perdilatal in doses of at least 6 mg. 4 times a day is the most effective vasodilator for the treatment of these conditions.**4**

1 Fowler, E. P. Ann. Otorhinolaryng., 1950, 59, 980.
2 Atkinson, M. Proc. roy. Soc. Med., 1946, 39, 807
3 Wilmot, T. J. Brit. med. J., 1957, 2, 1047.
4 Wilmot, T. J. Paper read on February 6th, 1959 at a Meeting of the Section of Otology, Roy. Soc. Med.

Perdilatal is available in tablets of 6 mg. as PERDILATAL FORTE in 50's, 250's and 1,000's.

* *PERDILATAL Brand of Buphenine Hydrochloride*

S&N

Smith & Nephew *Pharmaceuticals* Limited

WELWYN GARDEN CITY · HERTFORDSHIRE

Proceedings of the Royal Society of Medicine

Vol. 53
163

Section of Laryngology

President—MYLES L. FORMBY, F.R.C.S.

Meeting
November 6, 1959

The Maxillary Sinus

PRESIDENT'S ADDRESS

By MYLES L. FORMBY, F.R.C.S.
London

History.—The history of the maxillary sinus, its discovery and early description is of considerable interest. There is reliable evidence in the medical writings of the ancient Egyptians, between 3700 and 1550 B.C., that the structure of the superior maxilla was known to them. In most anatomical publications dealing with the skull, particularly those printed in Great Britain, it is customary to credit Nathaniel Highmore (1613–1685) with the first description of the maxillary sinus, now commonly called the antrum of Highmore (Fig. 1). There is, however, little doubt that this structure was known to Claudius Galen (A.D. 130–200) a Greek physician who dissected and practised in Rome and whose writings provided the basis for anatomical studies for the next thousand years. It was, however, the quite remarkable Italian genius Leonardo da Vinci (1452–1519) who first accurately described and beautifully illustrated that antrum named after Highmore. Leonardo's accomplishments were so varied and so astounding that his proper place in the history of science is apt to be missed. Accounts of his achievements are sufficiently absorbing to provide the material for a complete address. But as this would disturb the proper balance of my subject it is necessary to confine my remarks about Leonardo to some of the more interesting and instructive generalizations.

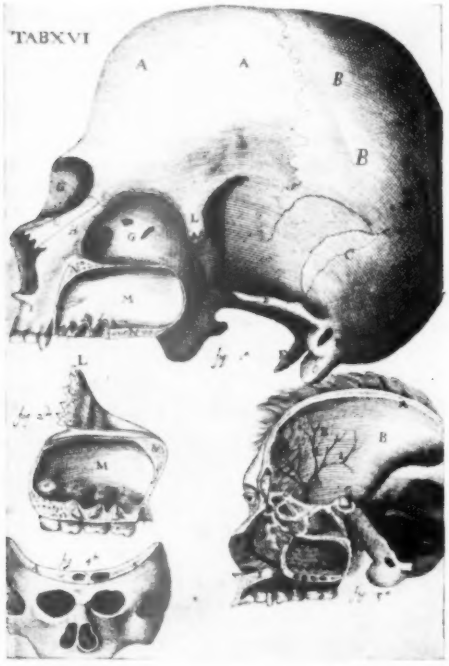


FIG. 1.—Maxillary antrum as illustrated by Highmore 1613–1685.

Leonardo, in general regarded as an artist, was born on April 15, 1452, the natural son of a peasant girl, his father being Ser Piero da Vinci, a well-known young notary. Following this affair Ser Piero was quickly induced to marry into a good Florentine family but a few years later, finding his wife childless and the young Leonardo a beautiful and promising child, he introduced his natural son into the esteemed family as an accepted member. Little is known of Leonardo's early education but it was not extensive and he was taught neither Latin nor Greek. During his youth there appears to have been ample opportunity to pursue those interests for which he had such remarkable aptitude. From the first he exhibited the biological approach, the essence of which is minute scrutiny of the parts of living things and of their workings. From 1466 to 1481 he worked most of the time in Florence with Verrocchio, a self-made all-rounder who approached the artistic problems of the human body from an anatomical point of view. In 1472, at the age of 20, Leonardo was admitted to membership of the Company of Painters in Florence.

In 1483, disguised as a musician, Leonardo took the road to Milan to take up a position as military engineer to Ludovico, then Duke of Milan. For the next four years nothing is recorded of his activities but these must have included many anatomical dissections. The first

FIG. 2.—Ventricles of the brain demonstrated by the introduction of wax (Leonardo da Vinci).
[From the Schloss Museum, Weimar]

dated reference in his notebooks was "On 2nd April, 1489, the book entitled 'Of the Human Figure'." This book has never been found.

Leonardo's approach to anatomy was one that can with advantage be studied and followed even to-day. During the years spent in Milan he performed a large number of anatomical dissections. Most were done in secret and at night. He decrees that it is better to look at an anatomical demonstration than to see drawings.. It is necessary to proceed by stages with sufficient bodies to render knowledge complete. Then repeat twice over in order to discover the differences. Skill in drawing is essential for representation and this combined with a knowledge of perspective. Also one must be versed in the methods of geometrical demonstration and of estimating the forces and strength of muscles. One must not be found wanting in patience.

Leonardo was well aware of the insufficiencies of contemporary methods of anatomical demonstration which were not much more than a post-mortem examination of the main viscera. He put forward his own idea of how dissection should be performed and illustrations made: "I counsel you not to cumber yourself with words unless you are speaking to the blind. Do not busy yourself in making enter by the ears things which have to do with the eyes."

FIG. 3.—Teeth, orbit and nasal sinuses as illustrated by Leonardo da Vinci 1452–1519.
[Reproduced by gracious permission of H.M. The Queen From the Royal Library, Windsor Castle.]

These utterances are worthy of the first illustrator of anatomy and their application in teaching is only being realized in our own century. It must not be imagined that the accuracy of Leonardo's drawings appeared straight away in their full perfection. Part of the fascination of studying his manuscripts lies in following their evolution from the crudities of contemporary conventionalism, to their final naturalist form.

While Leonardo's greatest contribution to anatomical knowledge was by illustration from dissection, with this alone he was not content. As the artistic motive gave way to the scientific he increasingly occupied himself with the interpretation of the function of the organs he drew. In his investigations of the muscles Leonardo was especially concerned with the discovery of their action. He laid down his first general principle, "The function of a muscle is to pull . . . When a muscle contracts its counterpart expands." With this generalization he anticipated the law of reciprocal excitation by the nerves, elaborated less than forty years ago by the late Sir Charles Sherrington, one of my teachers and one to whom I have, for many reasons, to be grateful.

Leonardo extended his anatomical research into the field of comparative anatomy. His motives for so doing were mixed. Dissection of

the horse was a basis for the equestrian statue of Duke Francesco. Dissection of birds was his way of beginning his enquiry into the problem of flight.

His interest in the anatomy of man and animals necessitated the development of methods for making his investigations and many ingenious techniques are described in his manuscripts. An example is the introduction of melted wax into the ventricles of the brain (Fig. 2). Exploring the nose and cheeks Leonardo decides "I wish to take away that part of the bone, the support of the cheek and to show through the opening revealed the breadth and depth of the two cavities which hide behind it. In the cavity above is hidden the eye, the instrument of sight, and in that below is the humour which nourishes the roots of the teeth" (Fig. 3).

Thus we can be left in no doubt to whom the credit for the first accurate description of the antrum of Highmore should go—Leonardo da Vinci.

Embryology and development.—In the human fœtus at the end of the fourth week five processes begin to sprout from the base of the primitive cerebral capsule. The central one of these, called the frontonasal process, has symmetrical right and left halves, each in turn having medial and lateral portions which project beneath the forebrain. Immediately on the caudal side of the frontonasal process is the first pair of processes, namely the right and left maxillary, and behind these again the right and left mandibular processes.

During the sixth week the maxillary process on either side grows inwards against the median and lateral portions of the frontonasal process thereby forming the anterior nares. By the end of the seventh week the anterior nares and the nasal septum are recognizable.

The maxillary process springs from the base of the mandibular process about the end of the fourth week and rapidly grows forward below the eye which it thus separates from the mouth. In addition to the easily visible surface growth the maxillary process forms the palatal plate which appears in the sixth week and grows inwards to fuse with its fellow of the opposite side about the tenth week. In this manner the two palatal plates form the whole of the hard palate, except the premaxilla, and in so doing separate the nasal and buccal cavities.

The maxilla at birth consists of a plate of bone in the floor of the orbit which is separated from the mouth by the tooth crypts. Each maxilla rests on the outer aspect of the lateral nasal process and helps to form the outer wall of the nasal cavity. In the third month of fœtal life the mucosa on the lateral wall of the nose starts to bud outwards, penetrates the cartilage of the lateral nasal process and begins to distend the maxillary process. At birth the sinus is only a shallow recess on the outer wall of the middle meatus of the nose and it continues to expand up to adult life. The other nasal sinuses are non-existent at birth. As the maxillary sinus expands backwards the posterior border of the maxilla, which contains the buds of the permanent molar teeth, undergoes a rotation downwards. In this way the teeth, which at first are in the back wall of the antrum, come to lie on the alveolar border (Fig. 4). Thus the normal development of the antrum has a direct bearing on the position and subsequent eruption of the upper teeth and in particular the last molar.

Anatomy.—In adult life the cubic capacity of the maxillary sinus is extremely variable ranging from 5 to 25 ml with an average of approximately 15 ml. Although roughly pyramidal in shape its outline in normal maxillæ shows wide variations as does both the thickness and density of its bony walls. Viewed from inside, the walls of the maxillary sinus are seen to be irregular and exhibit projections ranging from small ridges to large crescentic septa. These irregularities occur mostly on the floor and are much more frequent and conspicuous in large sinuses. Their presence results in the formation of pockets which often interfere with drainage. When the antral cavity is very large it extends into all parts of the maxilla and even into the premaxilla. In these instances the walls of the sinus are reduced to a thin layer of compact bone and the roots of many teeth form projections on its floor. Apart from this closer association with the upper teeth it is not my experience that the larger sinus is more prone to infection than the smaller one.

Physiology.—The maxillary sinuses, to some extent, participate in all the functions of the nose except that of olfaction. The resonance of the speaking and singing voice is greatly influenced by the state of the nasal cavities and the accessory sinuses and the most important of these latter are the maxillary sinuses. The antra are likewise concerned in the process of preparing the inspired air for reception into the lower respiratory tract which entails cleansing, warming and humidification. These processes, which are basically physical, depend on four important factors: (1) Air currents, (2) capillary blood flow, (3) cilia, (4) mucus.

The separate functions of each of these are well known. The normal physiology of the maxillary sinuses depends upon the integrity and activity of the microscopic cilia together with the healthy overlying mucous blanket. This is a fundamental requirement and one always to be remembered when considering the management

of any abnormality. It must be obvious, for example, that a maxillary antrum whose ostium is partially obstructed, as by a deformity of the nasal septum, is deprived of normal ventilation and in consequence cannot function properly. Similarly any general dyscrasia, such as a blood or liver disease, may alter the biochemical and physical properties of the antral mucus and so change adversely its physiological action.

Signs, symptoms, causation and diagnosis.—Time will not permit me to discuss the general clinical aspects, ætiology, symptomatology, radiography and diagnosis of the many abnormalities found in connexion with the maxillary sinus. I shall, however, consider in some detail certain aspects of pathology and treatment which have evolved from personal experience and which may be of assistance to others.

Pathology.—One of the first essentials when considering sinus disease is to appreciate the many variable factors that may play a part. It is common knowledge that some individuals are prone to catarrhal infections while others seem to exhibit a natural immunity. The differences between these two groups cannot be defined in terms appertaining either to the causation or the pathology of sinusitis. The vast number of organisms, virus or bacterium, the resistance of the patient and the many factors influencing the nasal physiology are only a few of the variables responsible for the complexity of the complete clinical picture and its accompanying pathology. The generally accepted macroscopic and microscopic alterations described in the textbooks cannot be more than a yardstick with which to measure pathological changes and broadly to classify cases. It is the meticulous consideration of every aspect of each individual case which will determine the success or failure of any particular procedure in the management of patients.

Perhaps the commonest pitfall and certainly a very frequent difficulty is allergy. Twenty-five years ago nasal manifestations of allergy were relatively uncommon whereas to-day it is the exception to find any current number of an ear, nose and throat journal which does not contain one or more articles on this subject. Out-patient clinics in this country and most others in the Western World, are full of allergic patients. This means that allergy has become increasingly important, and is an ætiological and pathological factor in an ever-expanding number of E.N.T. patients. It is, however, my belief that because of its common occurrence there is now a strong tendency to fix the label too readily and thereby permit other and equally important factors to be overlooked. For convenience the diagnosis "allergic rhinitis" is constantly made. I submit that there is no such entity as "allergic rhinitis" or "allergic sinusitis". The correct description is an allergic subject with symptoms of sinusitis or rhinitis.

It is generally accepted that allergic individuals tend to escape the common virus infections of the nose and in consequence are less susceptible to infective sinusitis. Personal experience has led me to doubt the accuracy of the latter part of this generalization. The pathological changes in the nasal and sinus mucous membrane which result from persistent allergic attacks eventually hamper and finally prevent the normal physiological functions. The first to be impeded is ventilation and if this is long continued ciliary action will be interrupted thus facilitating infection. It seems to me that not infrequently this superadded infection is in the first instance due to a virus rather than one of the better known non-filter-passing organisms. Not until we know more about the habits of viruses in the nasal sinuses and are able to isolate and cultivate them from the sinuses can a final answer be given to this hypothesis. At the present time our knowledge is so limited that in certain cases it is not possible to decide whether or not the pathological changes observed are: (1) Entirely due to allergy, (2) the result of infection superimposed on an allergic mucosa, or (3) primarily caused by an infection which produces symptoms indistinguishable from those found in allergic subjects.

It is well known, but occasionally forgotten, that maxillary sinusitis from whatever cause and whether acute or chronic is a mucosal disease. Strictly speaking any spread beyond the lining mucous membrane is a complication. Consequent upon the numerous ætiological factors, the pathological changes which occur, such as œdema, hyperæmia, hyperplasia, fibrosis or necrosis are well recognized. The secretory cysts found in the antrum and the antrochoanal polyp are equally well known. It is also generally accepted that in most patients whose antral lining is subjected to persistent irritation polypoid degeneration will ultimately develop. What is not so generally known is that in many of these cases collections of encysted pus or mucopus occur in the antral mucosa immediately deep to the superficial epithelial layers. Many of these are only microscopic in size but often they are clearly visible and contain up to one or two millilitres of frank pus. Cultures of this pus usually grow one of the variety of cocci commonly found in the nose. Quite often organisms will be visible in stained preparations but fail to grow on culture, a very usual experience with specimens aspirated from any nasal sinus and due to the bacteriostatic properties of the mucous secretions.

By far the most important feature of pathology in its relationship to treatment is whether or not

the changes which have taken place are irreversible spontaneously. That is to say the pathological condition is one which, if unaided surgically, will persist.

Treatment.—It has always been my firm conviction that the most important basic principle in treatment is that the method selected for any case should be that which is calculated to afford nature the maximum assistance in bringing about recovery. I count myself fortunate for having been guided by teachers who believed that without assistance from the natural defences complete success in treatment was virtually impossible. Equally it was repeatedly stressed that no surgeon, however brilliant as a diagnostician or operator, could kill organisms with a knife. This is not intended to imply that wonders cannot be achieved and lives saved by judicious therapeutics or skilful surgical intervention. It is, however, meant to stress that when deciding upon a method of treatment the most important consideration after the saving of life should be the restoration or preservation of function.

I now wish to apply these principles in the management of some of the abnormalities occurring in the maxillary sinus. Firstly, it is common knowledge that the antrum is affected to some extent in many cases of acute coryza, and that in nearly all these cases the catarrhal inflammation of the antral mucosa resolves completely without any form of treatment. On certain occasions simple measures designed to assist the natural defences—that is to say the normal physiology already referred to—will relieve unpleasant symptoms and also effect a more rapid resolution.

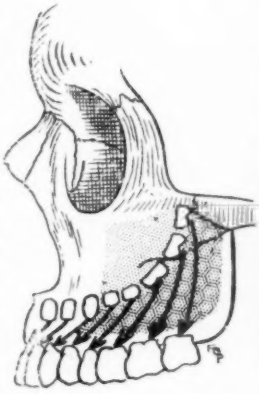


FIG. 4.—Diagrammatic representation of rotation of teeth as the maxilla develops.

FIG. 5.—Fluid in left antral cavity. Note the concave upper surface characteristic of a fluid level.

The next type of case is that in which the main defence mechanism, namely ciliary action, has ceased to function. This can occur as the result of the toxins produced by the invading organism, but more commonly is due to the bulk of material accumulated in the antral cavity (Fig. 5). In these cases, in addition to the antibiotic therapy necessary to overcome toxæmia, mechanical aid to the cilia is required. This can best be provided by simple lavage, the frequency of which has to be determined for each individual case. In the majority only one wash-out is needed. When dealing with children, or if for any particular reason such as previous attacks or a prolonged history, it is felt that several wash-outs will be necessary, it is my practice to introduce a polythene tube. This procedure enables the antral cavity to be cleared two or three times daily and with a minimum of discomfort to the patient.

Finally, surgical intervention in the management of sinus abnormalities is considered only when non-operative treatment has been unsuccessful. All aspects of the so-called conservative measures cannot be covered, but broadly these include: (1) Removal of any obstruction to normal sinus ventilation, e.g. deformity of the septum or polypi. (2) Reduction of the turbinates where these are causing constant blockage of the airway. This can be accomplished by outfracture and compression, submucosal sclerosing, ionization, cautery or partial submucous resection. (3) Complete allergic investigation and treatment. (4) Dental examination and treatment. (5) Treatment of any systemic disease. (6) Proetz displacement. (7) Antral irrigation.

On more than one occasion antral puncture and lavage has produced surprising and lasting improvement in a case considered to be entirely allergic. One cannot help wondering if such cases may not in reality be due to a virus infection of the antrum. By the process of exclusion the cases requiring surgical intervention are those: (1) Where non-surgical methods have failed. (2) Where cysts are present in the antrum or an antro-choanal polyp has formed. (3) With an antro-oral fistula. (4) With malignant disease.

The subject of malignancy is deliberately excluded from this Address. Taking the remaining three groups in reverse order it need only be said

FIG. 6.—Large simple cyst in the right antrum. Note the characteristic convex upper border.

that an antro-oral fistula is nearly always of dental origin. In all, some 10% of diseased antra are due to dental causes, and as a group they are the most satisfactory to treat. As has already been mentioned, the first essential is elimination of the dental infection. Following this all irreparably damaged antral mucosa should be carefully cleared, any diseased bone excised and adequate drainage into the inferior meatus of the nose provided. The fistula itself is closed at the time of the antral operation, a procedure which

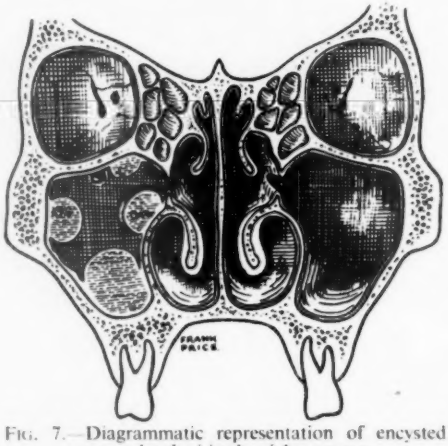


FIG. 7.—Diagrammatic representation of encysted pus and polypi in the right antrum.

requires special consideration for each case, and varies with the site and size of the opening.

Cases of antro-choanal polyp or simple cysts in the antral cavity (Fig. 6) causing symptoms should in my opinion be treated by the Caldwell-Luc operation.

Finally we are left with patients where non-surgical methods, which include the use of polythene tubes, have failed. In these the lining mucosa of the antrum has undergone irreversible pathological changes (Fig. 7). The correct treatment for these cases is the Caldwell-Luc operation. It must be admitted that there are examples where this radical operative procedure should if possible be avoided. This is particularly true in children. It is equally true that in general any operative procedure should be the last resort in treatment. My contention is that where surgery is inevitably the correct method of treatment the operation for chronic maxillary sinusitis is the Caldwell-Luc (Fig. 8). To-day

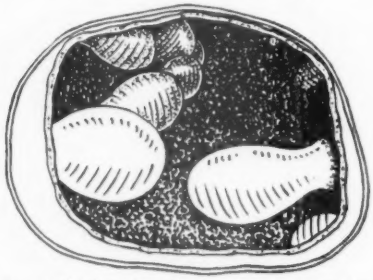
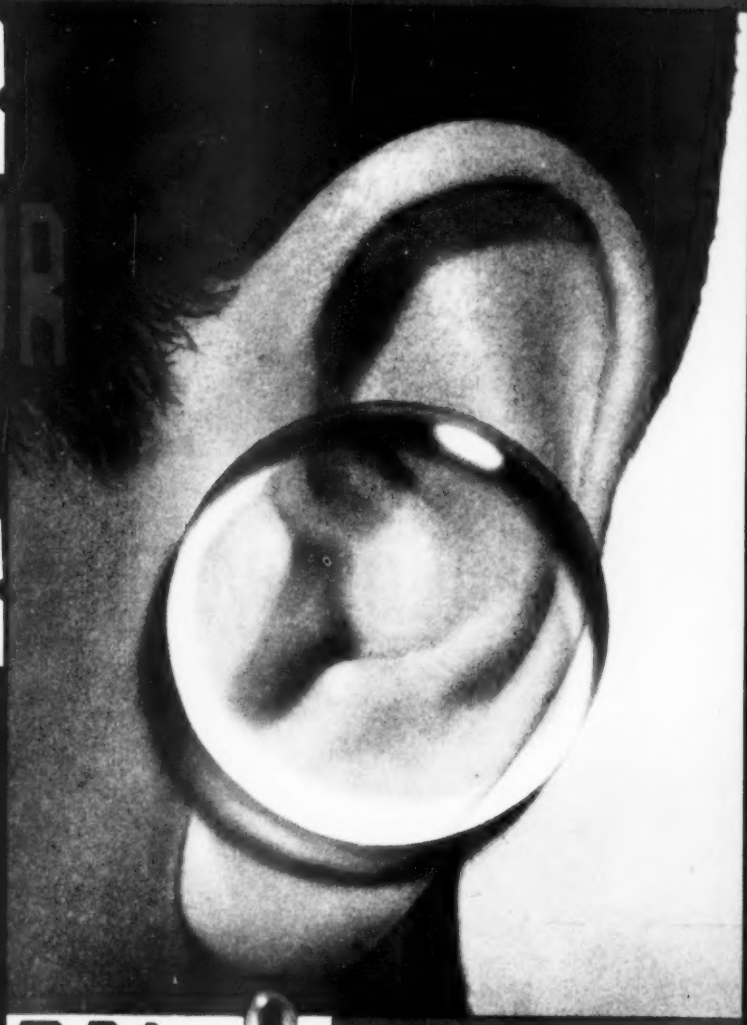


FIG. 8.—Multiple polypi in an antrum as seen through the Caldwell-Luc approach.

there is no place for the intranasal antrostomy. The advantages of an approach which affords easy access to and a clear view of the diseased tissues cannot be denied. It must also be accepted that the contraindications to the Caldwell-Luc approach are a legacy of the pre-antibiotic era. The post-operative symptoms to-day are few, and the complications extremely rare. If due attention is paid to the extent and position of the incision, the minimum amount of bone removed and no unnecessary trauma inflicted, the occurrence of cellulitis, osteitis, neuralgia or anæsthesia is extremely rare. It is admittedly an undesirable operation in childhood, but there are few, if any, cases of maxillary sinusitis in children and young adults which do not respond to non-surgical treatment.

In conclusion I must stress that unless polypi, encysted pus and areas of chronically diseased mucosa are removed from a diseased sinus, a normal and physiologically active lining will not reform. It is also important that the underlying antral periosteum should not be damaged.

CLEAR FOR THE EAR



PREDSOL

GLAXO

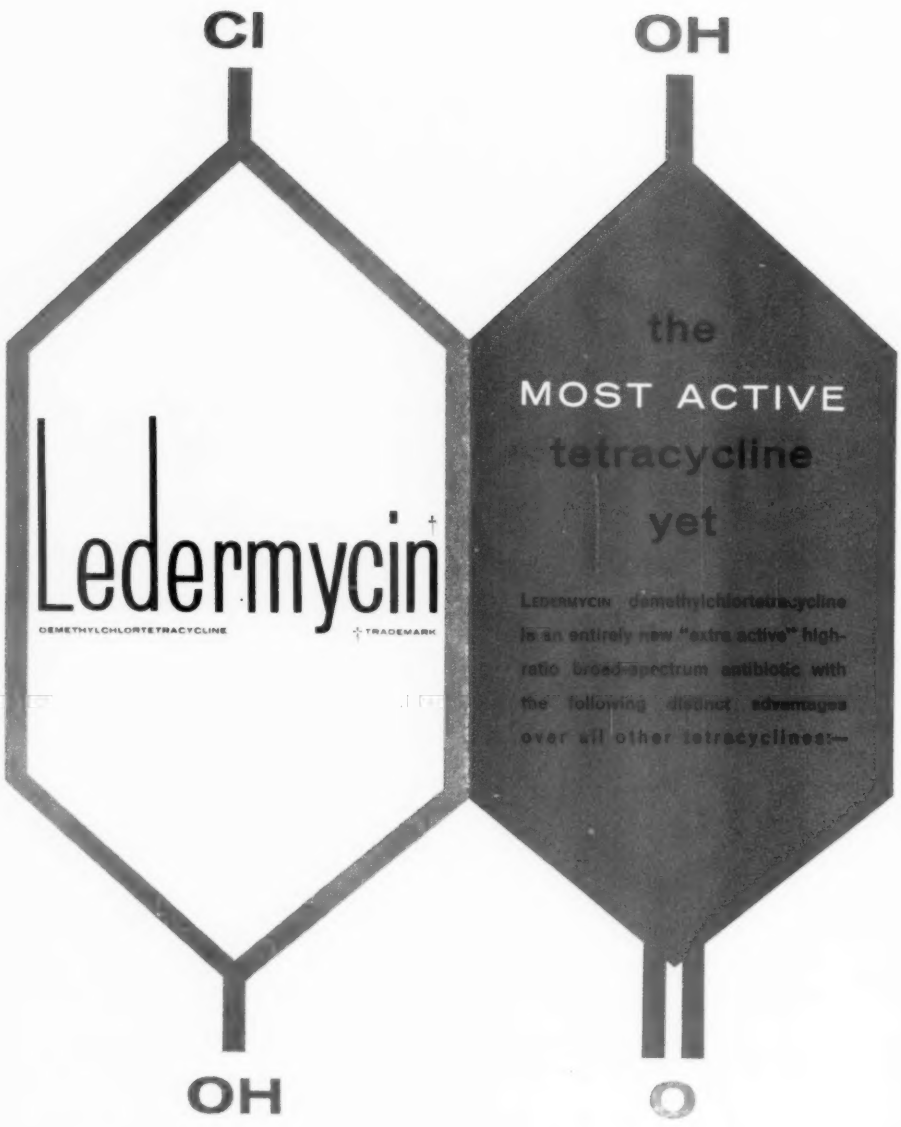
Predsol* Eye/Ear Drops contain no insoluble hormone particles. Predsol is water-soluble prednisolone phosphate

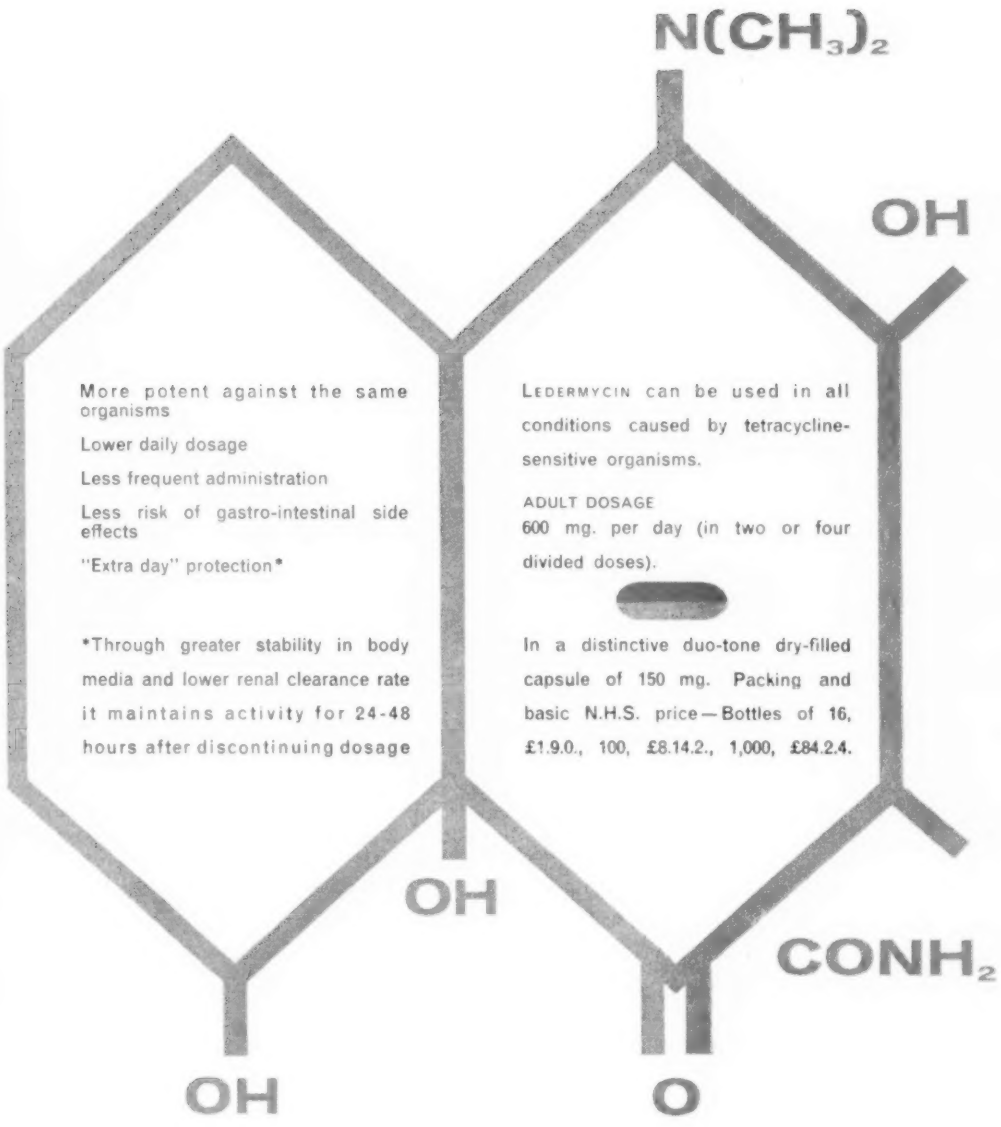
*Glaxo trade mark

GLAXO LABORATORIES LTD. GREENFORD, MIDDLESEX

BYRon 3434

Subsidiary Companies or Agents in most countries


Cl
OH
Ledermycin †
DEMETHYLCHLORTETRACYCLINE
† TRADEMARK
the
MOST ACTIVE
tetracycline
yet
LEDERMYCIN demethylchlortetracycline is an entirely new "extra active" high-ratio broad-spectrum antibiotic with the following distinct advantages over all other tetracyclines:—
OH
O



More potent against the same organisms

Lower daily dosage

Less frequent administration

Less risk of gastro-intestinal side effects

"Extra day" protection*

*Through greater stability in body media and lower renal clearance rate it maintains activity for 24-48 hours after discontinuing dosage

LEDERMYCIN can be used in all conditions caused by tetracycline-sensitive organisms.

ADULT DOSAGE
600 mg. per day (in two or four divided doses).

In a distinctive duo-tone dry-filled capsule of 150 mg. Packing and basic N.H.S. price—Bottles of 16, £1.9.0., 100, £8.14.2., 1,000, £84.2.4.

LEDERLE LABORATORIES
a division of
CYANAMID OF GREAT BRITAIN LTD London W.C.2

BARDASE

a comprehensive adjunct to the therapy of visceral spasm

Containing *belladonna alkaloids* to relieve spasm, *phenobarbitone* to relax nervous tension and TAKA-DIASTASE* (*Aspergillus orgzae enzymes*) to assist starch digestion, BARDASE* is an effective adjunct in many forms of gastro-intestinal disturbance.

BARDASE

Tablets: in bottles of 50 and 500
Liquid: in bottles of 4 and 16 fl. ozs.

* TRADE MARK

PARKE-DAVIS Parke, Davis & Company, *Inc. U.S.A. Liability Ltd.* Hounslow, Middx. Tel: Hounslow 2361

WPS 1050

Section of Surgery

President—RODNEY MAINGOT, F.R.C.S.

Meeting
October 7, 1959

THE following films were shown:

Total Gastrectomy for Œsophageal and Duodenal Stenosis.—Mr. R. H. FRANKLIN.

Portal Venography.—Professor R. MILNES WALKER.

Parotidectomy and the Frei Syndrome.—Mr. H. A. KIDD.

Injuries of the Hand.—Mr. P. CLARKSON.

Operative Treatment for Venous Ulcers.—Mr. F. B. COCKETT.

Meeting
November 4, 1959

DISCUSSION ON EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF MALIGNANT DISEASE

Dr. Arthur I. Spriggs (Oxford):

Malignant Cells in the Blood Stream

Introduction

Invasion of veins by carcinoma and the production of distant metastases by the blood stream is now recognized to be common. Willis (1952) noted that "neoplastic penetration into the venous blood stream is present in greater or less degree in at least 50% of all fatal cases of malignant growth". Venous invasion in a resected operation specimen is not necessarily fatal; for example, in Dukes and Bussey's (1958) series, of 197 cases of carcinoma of the bowel with venous invasion, 35·4% survived for five years. In animals, in order to produce a "take" of intravenously injected malignant cells, it has usually been necessary to introduce them in large numbers (Zeidman *et al.*, 1950). These facts suggest that circulating malignant cells may be destroyed. On the other hand some experimental work suggests that if the injected cells are really undamaged, only very few are necessary to produce metastases, and leukæmia has been transmitted with a single cell (Kahn and Furth, 1938; Hewitt, 1958).

With the recent revival of interest in the cytological diagnosis of cancer, there now are a number of centres where blood samples are being examined for circulating cancer cells. It is hoped that valid quantitative results will be obtained in different conditions and on the factors which alter their numbers.

Technique

Carcinoma cells have hardly ever been seen in direct blood films and concentration methods are necessary. Several techniques have been evolved. The "histological" approach was used by Pool and Dunlop (1934) and by Engell (1955). The red cells are hæmolysed and the remaining white cells are centrifuged, fixed, sectioned, and stained with hæmatoxylin and eosin. Sandberg and Moore (1957), of Buffalo, use a "hæmatological" method. The red cells are made to sediment rapidly by means of fibrinogen and the supernatant plasma is centrifuged. Films are made of the cell deposit and are stained by the methods used in hæmatology. As the only losses that occur are from tumour cells going down with the red cells or adhering to glass, most of those present will probably be seen in the films. This method poses the fewest difficulties of interpretation, because a trained hæmatologist already knows the cells normally present, including cells such as megakaryocytes which might be mistaken for tumour cells. Moreover, the preparation causes no morphological changes in the cells.

The method which theoretically permits the least loss of tumour cells is that in use at Bethesda (Pruitt *et al.*, 1958; Malmgren *et al.*, 1958). The red cells and many of the white cells are destroyed with streptolysin-O, and the whole specimen is then passed through Millipore filters, which are then fixed, stained by the Papanicolaou method and mounted in their entirety. Unfortunately, the largest pore size available still holds back practically all the white cells, and the material for study is in our experience no better preserved or easier to interpret than with the "histological" method. In an attempt to concentrate the tumour cells with the least possible admixture of white cells Warren Cole and his associates in Chicago (Roberts *et al.*, 1958) use an albumin flotation technique. After sedimenting the red cells with fibrinogen, they layer the plasma containing the white cells on to an albumin solution of specific gravity 1·065, and centrifuge

until all the heavier cells are deposited. The tumour cells are lighter, and this layer is removed and stained by Papanicolaou's method. Thus at the risk of losing some of the cells during the procedure, they obtain very concentrated preparations which are much less trouble to scan than those produced by other methods. Dr. R. F. Alexander and I have compared an albumin flotation method with the Buffalo method after adding known numbers of human tumour cells to blood samples. Although the albumin method appears more satisfactory, in that tumour cells are seen alone on a background of platelets, the actual numbers recovered are a good deal smaller. We therefore think that the Buffalo method is the best for small samples of blood. However, if volumes larger than 5 ml are to be used the Buffalo method becomes impossibly laborious, owing to the large numbers of films produced, and an albumin concentration method on large volumes of blood may turn out to be the method of choice.

Before describing the findings of the various workers in this field, it is necessary to examine the evidence on which cells from the blood are identified as malignant. When numerical data are presented, these are not readings on an instrument with a known error. They are opinions, whose validity depends entirely on the experience and temperament of the observer. In diagnostic exfoliative cytology, we come to an opinion about the cells and try to make an accurate diagnosis. We then follow up the cases, and any mistaken diagnoses will eventually come to light and our opinions can be corrected. Unfortunately, in the present type of study mistakes are not so easily detected. Unusual cells are apt to occur in cancer, and if these are misdiagnosed we can never be proved wrong. Moreover, we are not in this case coming to a decision which is valid only for one patient; we are collecting biological data which are meant to cast light on the behaviour of malignant growths in general, and for this purpose even stricter rules of evidence need to be applied. In particular, a thorough familiarity with the blood cells of patients without carcinoma is essential—not only the cells of conventional hæmatology, but those which circulate in very small numbers and can only be found by concentration techniques. Even then, results obtained by this method are likely to carry rather less conviction than biological tests for actual tumour production by inoculation of blood samples, such as can be used in animal work (Goldie *et al.*, 1953).

Occurrence of Tumour Cells in Blood

Table I shows the proportion of cases of malignant disease in which tumour cells are supposed to be identifiable, according to the different authorities. The samples have usually been of two kinds; arm vein blood from cases of cancer, and local venous blood from the drainage area of malignant tumours, mostly gastro-intestinal.

TABLE I.—PERCENTAGES OF CASES OF CARCINOMA IN WHICH TUMOUR CELLS WERE FOUND IN THE BLOOD

	Peripheral	Regional
Pool and Dunlop (1934) ..	42	
Engell (1955)	50	59
Fisher and Turnbull (1955) ..		32
Moore *et al.* (1957)	52	55
Roberts *et al.* (1958)	16*	29
Pruitt *et al.* (1958)	39	
Fletcher and Stewart (1959) ..	17	39

*Mostly early cases

It has often been noted that supposedly malignant cells can be found in the blood of patients with operable tumours. Engell (1959) has followed up his cases and finds that 51% of those surviving for five years or more were originally said to have circulating tumour cells at the time of operation. He deduces from this that the finding of tumour cells is of little prognostic significance, and that the cells in these cases had perished in the blood stream. The effect of manipulation of a malignant tumour at the time of operation has been studied by several workers. Engell (1955) and Sandberg and Moore (1957) found no difference in the numbers of circulating tumour cells before and after manipulation. The Chicago group, however, have published graphs showing in a few cases a substantial rise in the numbers of tumour cells during surgical operations, and a fall to zero after removal of the tumour (Roberts *et al.*, 1958). This is one of the arguments in favour of the idea that cytotoxic drugs should be given at the time of operation in order to reduce the chances of metastasis (Cole *et al.*, 1958; Shimkin and Moore, 1958). As this prophylactic measure is admittedly liable to produce complications of its own, particularly bleeding and infection in the post-operative period, it seems most important to have the fullest possible confirmation of the data on which this suggestion rests.

Dr. R. F. Alexander and I have for some time been studying the morphology of white cells seen in concentrates from the blood, not only from cases of malignant disease but also from patients suffering from other illnesses (including leuko-erythroblastic anæmia due to myelosclerosis) and from normal persons. The method used was similar to that of Sandberg and Moore (1957), except that we prefer dextran to fibrinogen for sedimentation. The whole white cell deposit is

spread in films and all the films are examined. We have been impressed with the variety of non-malignant cells which can be found occasionally in small numbers in the blood. Some of these cells are familiar from the bone-marrow; for instance, megakaryocytes can be found in nearly every sample and are usually of a small variety. Sometimes they have a single entire nucleus and a narrow cytoplasm, and by some of the other techniques would be very difficult to distinguish from tumour cells. Moreover, they are particularly numerous in leuko-erythroblastic anæmia, of which a common cause is advanced malignant disease. Being polyploid, if they are seen in mitosis they look particularly "malignant". Türk cells (i.e. plasma cell series) are always present, and the largest forms might cause confusion. They often divide in the circulation, but the mitoses are not abnormal. These are presumably the same as the cells which Cronkite and his associates (Bond *et al.*, 1958) find to be capable of DNA synthesis in the circulating blood. Endothelial cells are a well-known trap for the unwary, especially as they form aggregates with nuclei which sometimes vary in size. There is room for much more study of the variations of these cells in pathological conditions. Macrophages are occasionally seen, and some remarkable examples are shown by Sandberg *et al.* (1959). Finally we have sometimes found cells which we could not identify, but which did not correspond with familiar varieties of malignant cell. When such cells occur in cancer cases there is a temptation to label them as malignant, but without further evidence this is unjustifiable.

In a series of 100 cases of malignant disease presented to the Pathological Society in July 1959 by Dr. Alexander only 7 were found to have acceptable tumour cells in 4-ml samples. These cases included a malignant melanoma and a malignant synovioma, both with multiple blood-borne metastases. The remaining 5 had carcinomas. In 3 of these the positive samples were from the antecubital vein (2 with carcinoma of the bronchus, and 1 of the breast). 1 with carcinoma of the bronchus had tumour cells in pulmonary vein blood, and 1 with carcinoma of the stomach in a vein close to the tumour. All of these patients are dead, none of them having been found operable.[1] In our series, therefore, there has been no evidence of a general tendency for operable tumours harmlessly to shed malignant cells into the veins; on the other hand, we find the presence of tumour cells to be associated with a bad prognosis.

As our findings differ so strikingly from those of all other authorities, some explanation must be sought for the discrepancy. There are several possibilities, and without seeing all the preparations concerned it is impossible to judge. However, it is my strong suspicion that tumour cells have been over-diagnosed in the American and Danish series. Until we have much more information about the other uncommon cell types which can be found in the blood, I consider that no firm conclusions about the behaviour of human cancer should be drawn from any of this work.

[1]In one operable case of carcinoma of the bronchus collections of unusual cells were found in pulmonary vein blood, which at first were thought to be malignant. It is now evident that they were pericardial mesothelial cells, whose presence was due to accidental aspiration of pericardial fluid during collection of the specimen.

REFERENCES

Bond, V. P., Cronkite, E. P., Fliedner, T. M., and Schork, P. (1958) *Science*, **128**, 202.

Cole, W. H. *et al.* (1958) *Bull. N.Y. Acad. Med.*, **34**, 163.

Dukes, C. E., and Bussey, H. J. R. (1958) *Brit. J. Cancer*, **12**, 309.

Engell, H. C. (1955) *Acta chir. scand.*, Suppl. 201.

—— (1959) *Ann. Surg.*, **149**, 457.

Fisher, E. R., and Turnbull, R. B. (1955) *Surg. Gynec. Obstet.*, **100**, 102.

Fletcher, W. S., and Stewart, J. W. (1959) *Brit. J. Cancer*, **13**, 33.

Goldie, H., Jeffries, B. R., Jones, A. M., and Walker, M. (1953) *Cancer Res.*, **13**, 566.

Hewitt, H. B. (1958) *Brit. J. Cancer*, **12**, 378.

Kahn, M. C., and Furth, J. (1938) *Proc. Soc. exp. Biol., N.Y.*, **38**, 485.

Malmgren, R. A., Pruitt, J. C., Del Vecchio, P. R., and Potter, J. F. (1958) *J. nat. Cancer Inst.*, **20**, 1203.

Moore, G. E., Sandberg, A., and Schubarg, J. R. (1957) *Ann. Surg.*, **146**, 580.

Pool, E. H., and Dunlop, G. R. (1934) *Amer. J. Cancer*, **21**, 99.

Pruitt, J. C., Hilberg, A. W., and Kaiser, R. F. (1958) *New Engl. J. Med.*, **259**, 1161.

Roberts, S., Watne, A., McGrath, R., McGrew, E., and Cole, W. H. (1958) *Arch. Surg., Chicago*, **76**, 334.

Sandberg, A. A., and Moore, G. E. (1957) *J. nat. Cancer Inst.*, **19**, 1.

——, ——, and Schubarg, J. R. (1959) *J. nat. Cancer Inst.*, **22**, 555.

Shimkin, M. B., and Moore, G. E. (1958) *J. Amer. med. Ass.*, **167**, 1710.

Willis, R. A. (1952) The Spread of Tumours in the Human Body. 2nd ed. London.

Zeidman, I., McCutcheon, M., and Coman, D. R. (1950) *Cancer Res.*, **10**, 357.

Professor Gilbert Causey (London):

Electron Microscopic Observations on the Mucous Membrane of the Stomach and of Exfoliated Cells

The examination of the secretions and excretions of the human body as an aid to diagnosis is as old as medicine itself, and it is not surprising that each new technical advance has been applied to these materials. This paper deals with the first application, as far as I am aware,

of the electron microscope to the diagnosis of lesions of the stomach.

Before applying this technique to human material an attempt was made to distinguish morphological differences in the electron microscopic picture of normal and neoplastic cells from artificially produced tumours in animals.

Fig. 1 shows a fairly high magnification of the nuclear surface in a normal Schwann cell from the sciatic nerve of a mouse. It can be seen that at the junction between the nucleus and the cytoplasm there are two electron dense lines in this preparation, the one (NS) on the nuclear side and the other (CS) on the cytoplasmic side. These two lines run roughly parallel over considerable distances. One nuclear pore (NP) is shown where the continuity of the lamellæ is interrupted. This smoothness of contour seemed to be typical of normal resting cells, but is not complete, for in addition to the irregularities produced by nuclear pores other irregularities have been correlated with the formation of mitochondria at or from the nuclear surface (Causey and Hoffman, 1955; Barton and Causey, 1958; Hoffman and Grigg, 1958; Brandt and Pappas, 1959). The interest in the present connexion is that when such cells are stimulated either to physiological activity by section of the nerve trunk or to neoplastic change by the injection of the carcinogen dimethyl benzanthracene there is a gross increase in the irregularity of the nuclear-cytoplasmic interface.

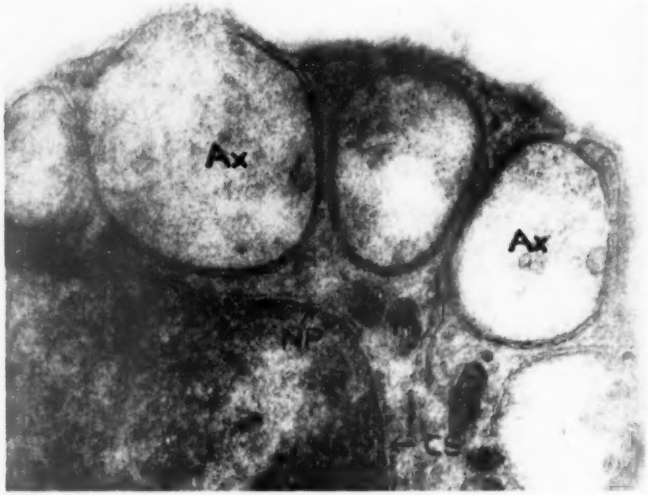


FIG. 1.—The nuclear surface of a normal Schwann cell. Electron dense lines NS and CS are indicated on the nuclear and cytoplasmic sides of the nuclear membrane. Nuclear pore (NP); mitochondria (M); axons (Ax). × 56,000.

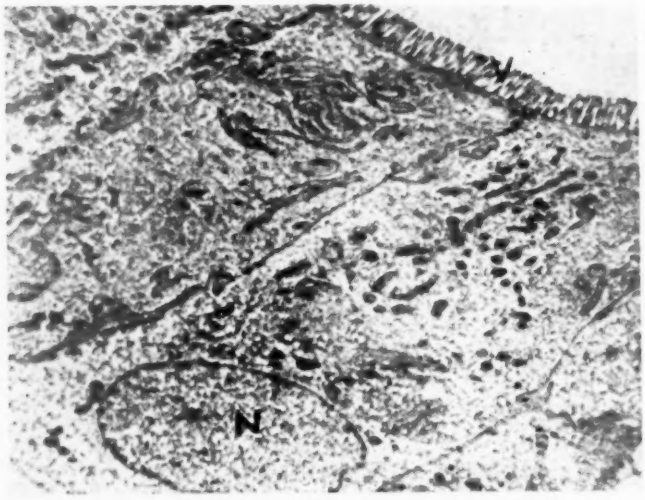


FIG. 2.—Surface cells from the mucous membrane of the human pyloric antrum. Showing villæ (V), nucleus (N) and cytoplasmic inclusions. × 4,500.

The examination of similar nuclear surface changes in man was made possible by the kindness and close collaboration of Mr. Harold Burge. Fig. 2 shows a low-power electron micrograph of a few cells from the human gastric mucous membrane. The tall columnar cells have a villous border at the side abutting on the duct towards the upper right (this tiny piece came from the pyloric antrum). This villous border tends to be less well marked as the lumen of the stomach itself is approached, and the boundaries

between the cells become drawn out until, when shed, these cells appear to adopt the overall villous appearance shown in Fig. 3. At the base of one of the mucosal cells in Fig. 2 a smooth, oval nucleus is shown, and between the basally placed nucleus and the villous border the Golgi zone, the endoplasmic reticulum and numerous mitochondria can be distinguished.

Specimens for electron cytology were obtained by washing out the stomach with 100 c.c of Ringer's solution after removal of the stomach content through a stomach tube. The fluid obtained from the gastric lavage was kept in ice until it could be spun down and the pellet obtained was then fixed in 1% buffered osmium tetroxide for half an hour. After further centrifugation the pellet of osmium-fixed material was then treated by the routine methods of our laboratory for electron microscopy, that is dehydration in graded alcohols, embedding in methacrylate, thin sectioning of the block on a Cook and Perkins microtome, and examination in a Metropolitan-Vickers microscope, either the EM4 or the EM6 model.

Fig. 3 shows a typical field of a thin section from such a pellet obtained by gastric lavage. Parts of three mucosal cells are shown, together with various smaller cellular structures. The crenated border of the mucosal cell cytoplasm is clearly shown, and the great loss of cytoplasmic detail as compared with the cells of Fig. 2 is also obvious. The nuclear surface of the central cell of the field is seen to be round and smooth. One point that was immediately gratifying was that in these preparations we have always found plenty of mucosal cells for examination.

At least 50 mucosal cells have been examined from each specimen and the nuclei of these 50 cells when they were present in the section have been classified as "normal" or "abnormal" according to the subjective estimate of their nuclear surface. An example of an "abnormal" nucleus is shown in Fig. 4; the nucleus is round but the surface is very irregular, the outer lamina of the nuclear membrane coming away from the inner lamina. Frequently "abnormal" nuclei show not only this fine irregularity but also a gross, overall convolution of the nuclear surface. The nuclear counts obtained in this way from

FIG. 3.—A field from a thin section of mucosal and other cells obtained by gastric lavage from a normal stomach. Nucleus (N). × 4,500.

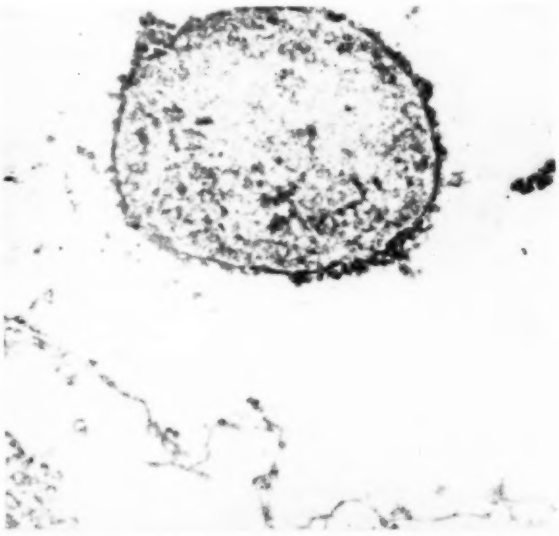


FIG. 4.—The nucleus and a small portion of cell surface of a mucosal cell from a pellet obtained by gastric lavage from a patient with gastric carcinoma. × 7,500.

TABLE I.—DISTRIBUTION OF "NORMAL" AND "ABNORMAL" NUCLEI IN 50 MUCOSAL CELLS FROM ELECTRON MICROGRAPHS OF GASTRIC WASHINGS

Case No.		Mucosal cells	"Normal" nuclei	"Abnormal" nuclei
1		50	18	1
3		50	22	0
5	No	50	16	1
8	stomach	50	8	1
9	lesion	50	13	0
11		50	11	2
4		50	10	9
7	Gastric	50	17	9
12	carcinoma	50	8	5
13		50	3	13
15		50	8	10
10		50	6	10
16	Benign	50	4	9
17	ulcer	50	1	16
26		50	3	11

15 patients are shown in Table I. The difference in these semi-quantitative estimates between the nuclear picture obtained from ulcers and carcinomas is strikingly and significantly different from the washings from patients with no stomach lesion. But it is too early to draw any conclusion on the differences between carcinomas and simple ulcers. Indeed, further work since this paper was read has made it clear that a considerable proportion of the mucosal cells may be from the œsophagus or oropharynx.

Acknowledgments.—I am greatly indebted to Mr. Harold Burge, Dr. A. A. Barton and Mr. S. A. Edwards for their help and to the British Empire Cancer Campaign for their support.

REFERENCES

BARTON, A. A., and CAUSEY, G. (1958) *J. Anat., Lond.*, **92**, 399.
BRANDT, P. W., and PAPPAS, G. D. (1959) *J. biophys. biochem. Cytol.*, **6**, 91.
CAUSEY, G., and HOFFMAN, H. H. (1955) *Brit. J. Cancer*, **9**, 666.
HOFFMAN, H. H., and GRIGG, G. W. (1958) *Exp. Cell Res.*, **15**, 118.

Dr. J. Bamforth (London) [*Abstract*]:

I propose to limit my remarks almost entirely to cytological examination of sputum and prostatic secretion. In the majority of cases, carcinoma of the lung can be diagnosed by clinical and radiographic examination together with bronchoscopy and removal of suspected tissue for histological examination. In about 30% of cases, however, the tumour is peripheral and beyond the reach of the bronchoscope. A diagnosis of bronchial carcinoma depending upon clinical and radiological evidence only is less certain and in these cases a correct positive report of the finding of malignant cells in the sputum or bronchial secretion, and further of the type of malignant cells present, may be important.

[Lantern slides were shown of an oat cell, squamous cell and alveolar cell carcinoma, in which diagnoses were made by cytological examination after negative bronchoscopic examinations.]

I doubt if there is any cytologist who has never given a false positive report and it is difficult to see how these can be entirely avoided. I think, however, that with continued practice and experience these mistakes can be reduced to a very small percentage. It is essential that as many specimens of sputum as possible should be examined cytologically even in cases easily diagnosable by the bronchoscope. Careful comparison should be made between the suspected cells found in the sputum and those seen subsequently in the histological sections of the growth made from a biopsy, from operation, or from post-mortem examination. There are a number of different types of malignant cells in bronchial secretion and by constant practice these can be identified and standards established. In the case of the bronchial secretion I would agree that much better results can be obtained by the examination of bronchial mucus removed by aspiration than from saline washings of the bronchi.

Of more than 500 specimens of prostatic secretion obtained by massage about one-third have proved to be inadequate. The smear preparations did not contain sufficient prostatic epithelial cells for critical examination: in many cases there was none. In some cases of scirrhous carcinoma malignant cells cannot be found in the smear but this applies only to a minority of cases of prostatic cancer. It seems that in many cases even in experienced hands there is difficulty in obtaining a satisfactory specimen. The appearances of the groups of malignant cells found in the smears vary considerably in different cases and cytological patterns can be recognized, which have been confirmed histologically following either biopsy, prostatectomy or post-mortem examination. It is possible that different cell types may vary in their sensitivity to endocrine therapy.

[A number of lantern slides showing the different types of malignant cells found in prostatic smears were shown.]

There are great difficulties in the follow-up of cases suspected of having carcinoma of the prostate owing to the age at which this condition occurs and to the fact that in many cases there is no biopsy and operation is neither contemplated nor performed. In spite of the initial difficulty in obtaining a suitable preparation I think that cytological diagnosis of prostatic cancer, judged by the results to date, can be a valuable aid in diagnosis.

BIBLIOGRAPHY

BAMFORTH, J. (1958) *Ann. R. Coll. Surg. Engl.*, **23**, 248.
——, and OSBORN, G. R. (1958) *J. clin. Path.*, **6**, 473.
DUDGEON, L. S., and WRIGLEY, C. H. (1935) *J. Laryng.*, **50**, 752.
FERGUSSON, J. C., and GIBSON, E. C. (1956) *Brit. med. J.*, i, 822.
HERBUT, P. A., and LUBIN, E. N. (1947) *J. Urol.*, **57**, 542.
OSBORN, G. R. (1958) In: Cancer. Ed.: R. W. Raven. London: 3, 476.
PETERS, H. (1950) *Cancer*, **3**, 481.

Dr. R. Schade (Newcastle-upon-Tyne):

Gastric Cytology

The long-term results of gastric surgery for carcinoma appear even to-day, seventy-eight years after Billroth performed his first gastrectomy, most unsatisfactory. It is, of course, true that the immediate post-operative outlook of the patient with gastric cancer has been markedly improved but the figures of ten-year survival after gastric surgery for carcinoma are still most disappointing. So far, radiology and gastroscopy have been the most important procedures for the diagnosis of gastric carcinoma. I venture to say that they have failed to demonstrate the early lesion of gastric carcinoma—the so-called surface carcinoma. Excision of this type of carcinoma may, one hopes, result in a cure.

Already during Billroth's lifetime attempts were made to diagnose carcinoma of the stomach by cytological methods. Many publications report on the presence of mucosal fragments in gastric lavage specimens. Their diagnostic value was, however, considered to be doubtful. Marini (1910) published a detailed study of cells found in gastric lavage specimens. His findings and descriptions of the desquamated cells of the stomach in health and disease were extremely accurate and are still acceptable to-day. He convinced himself of the usefulness of gastric cytology and envisaged that it would become a generally accepted technique for the diagnosis of gastric cancer. His work fell into oblivion. Papanicolaou's publications (Panico *et al.*, 1950) created a new interest in cytodiagnosis. It is, therefore, not surprising that this technique has been taken up for the diagnosis of gastric cancer.

Some years ago, Professor John Gilmour in my hospital asked the pathological department to evaluate gastric exfoliative cytology in the diagnosis of carcinoma. It became, therefore, necessary to study histologically those conditions which are associated with exfoliation of mucosal cells. It was already known, mainly as the result of Boas's work (1925), that the inflamed gastric mucosa sheds cells more readily than the normal mucosa. This we could confirm. Exfoliation can also be observed in carcinoma and particularly in cases with small, actively growing tumours. Raskin *et al.* (1958) observed that in malignant conditions exfoliation is more marked than in inflammatory conditions and that, therefore, large numbers of cells can be expected in lavage fluid. This observation was again confirmed by us.

Cytodiagnosis is of recent origin but already many methods are in existence for the collection of gastric cellular material, falling into two main groups: (1) Methods depending on mechanical removal of cells, such as Papanicolaou's abrasive balloon, Henning's Zelltuppsonde (Henning, 1952) and Ayre's gastric brush (Ayre and Oren, 1953). (2) Methods depending on a simple lavage with or without mucolytic agents.

We decided to use a simple saline lavage because of the gentleness of its action and the ease of application. The method used by us was first described by Graham *et al.* (1950). Certain precautions have to be taken when using the lavage method. One must feel certain that the sample for examination is representative and for this reason it is desirable to have one reliable person to perform the lavage. This is, however, impracticable in a large hospital. We have, therefore, adopted the principle of several lavages performed on two or three consecutive days. If their cytological findings are comparable, the result can be considered reliable. The simple lavage washes out the cells already free or detaches those just about to be desquamated. We consider it of no value to combine lavage with abrasive methods such as the abrasive balloon. On the contrary, it is our

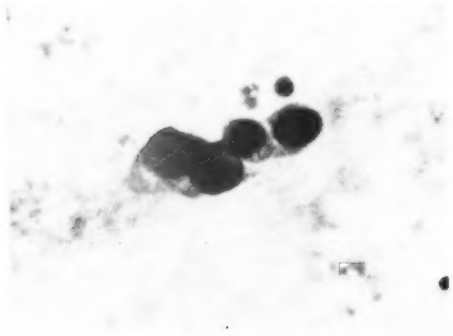


FIG. 1.

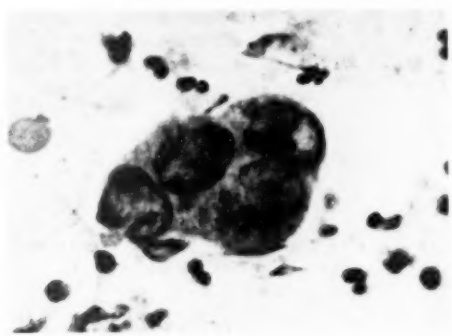


FIG. 2.

FIGS. 1 and 2.—Groups of malignant cells from two cases of adenocarcinoma of stomach.

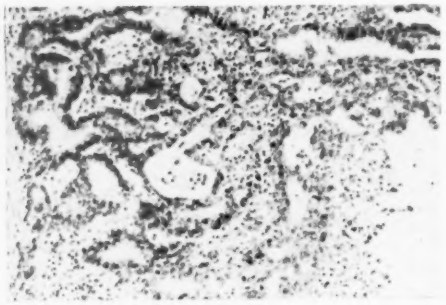


FIG. 3.—Adenocarcinoma of stomach. The tumour is confined to the gastric mucosa and shows nowhere penetration of the muscularis mucosæ. No lymph-node metastases present. The tumour was diagnosed by cytology; gastroscopy and barium meal were negative.

opinion that a combination of the two methods may result in difficulty of interpretation as the artificially abraded cells look different from exfoliated cells. We found it no advantage to use a lavage fluid containing mucus solvents such as papain or α-chymotrypsin.

So far more than 3,500 patients have been examined by this method. In a series of 522 consecutive cases which had one or several cytological examinations and subsequently a partial gastrectomy which allowed us to compare cytological and histological findings, the overall accuracy achieved amounted to 96·4%. The 522 consecutive cases consisted of nearly an equal number of cases operated on for gastric carcinoma and for gastric, duodenal and gastroduodenal disease such as peptic ulceration. The cancer group showed an accuracy of 97·6%, the other group an accuracy of 94·8%. The last figure indicates that some false positive cytological results were given. Histological study of those cases can give the answer to the incorrect cytological diagnoses. In those cases regenerating epithelium at the edges of ulcerated areas, or severe gastritic changes, appeared so highly atypical that the histological appearance left some doubt about the nature of the lesion.

The false negatives in the cancer group are commonly the result of inadequate cytological material. I have personally no doubt that false negative cytological results in cancer cases are easier to avoid than the false positive gastrocytograms; indeed they can be eliminated. More important than the above figures is the fact that 31 cases of surface carcinoma could be detected in a series of 258 cases of carcinoma. Of these, 18 cases were entirely unsuspected clinically and radiologically.

To conclude, the simple saline lavage appears useful for the study of gastric inflammatory disease and neoplasia. It gives accurate results provided the technique for obtaining cellular material is strictly controlled.

REFERENCES

AYRE, J. E., and OREN, B. G. (1953) *Cancer*, **6**, 1177.
BOAS, J. (1925) Diagnostik und Therapie der Magenkrankheiten. Leipzig.
GRAHAM, R., *et al.* (1950) The Cytologic Diagnosis of Cancer. Philadelphia.
HENNING, N. (1952) *Dtsch. med. Wschr.*, **77**, 1.
MARINI, G. (1910) *Clin. med. ital.*, **2**, 65.
PANICO, F. G. *et al.* (1950) *J. Amer. med. Ass.*, **143**, 1308.
RASKIN, H. G., KIRSNER, J. B., and PALMER, W. L. (1958) In: Modern Trends in Gastroenterology. 2nd ser. Ed.: F. Avery Jones. London; p. 76.

Meeting
December 2, 1959

THE following specimens were shown:

Meconium Ileus in Twins.—Mr. D. VELLACOTT.

Subclavian Aneurysm Secondary to Tuberculous Glands.—Mr. G. E. MOLONEY.

Two Cases of Florid Fen Pathology.—Mr. BRIAN TRUSCOTT.

Multiple Infarcts of the Small Intestine.—Mr. J. BRADBEER (for Mr. A. M. DESMOND).

Two Cases of Aortic Obstruction Syndrome.—Mr. A. M. DESMOND.

Papillary Carcinoma of Ureter.—Mr. F. G. ELLIS.

Acquired Megacolon Following Side-to-side Ileo-sigmoidostomy.—Mr. GRAHAM HARRIS (for Mr. J. O. ROBINSON).

Gastric and Duodenal Ulcers Associated with Thrombosis of Coeliac Axis.—Mr. HENRY KIDD.

Amelanotic Malignant Melanoma in a Child.—Mr. M. J. KILLINGBACK (for Mr. F. A. HENLEY).

Leiomyoma of Duodenum.—Mr. P. KNIPE (for Mr. ALAN HUNT).

Adult Hypertrophic Pyloric Stenosis.—Mr. M. WOO-MING (for Mr. L. P. LE QUESNE).

Carcinoma of Rectum—Ulcerative Colitis.—Mr. VICTOR NGU (for Mr. H. H. G. EASTCOTT).

Carcinoma of Duodenum.—Mr. R. H. P. OLIVER (for Mr. H. R. I. WOLFE).

Dumb-belled Leiomyoma of Stomach.—Mr. H. R. I. WOLFE.

(1) Three Cases of Nine Years' Survival after Laryngo-œsophago-pharyngectomy for Carcinoma of the Hypopharynx. (2) Ten Years' Survival after PartialPharyngectomy for Carcinoma of the Oropharynx.—Mr. R. W. RAVEN.

Massive Carcinoma of Pelvic Colon Involving Transverse Colon and Bladder with Vesico-colic Fistula.—Mr. P. T. SAVAGE.

Hepatoma in a Child of 13 Treated by Right Hemihepatectomy.—Mr. RODNEY SMITH.

when conventional therapy
cannot reach the emotionally
troubled patient with somatic illness

Fentazin

PERPHENAZINE

makes the patient more accessible

FENTAZIN TABLETS contain 2mg., 4mg., or 8mg. perphenazine, in bottles of 50 and 500. FENTAZIN INJECTION contains 5mg. perphenazine in 1 c.c. Boxes of 5 and 100 ampoules of 1 c.c.

AH101 'Fentazin' is a trade mark

ALLEN & HANBURYS LTD *Bethnal Green London E.2*

arm muscle spasm
stiff neck
low back pain
sciatica
leg muscle spasm
muscle pain

when skeletal muscle spasm causes pain

relief of pain by relaxation of muscle in spasm

now-a new concept NORFLEX

relaxes only the muscle in spasm

Norflex rapidly and effectively relieves muscle pain by relaxing the affected muscle. Norflex is more satisfactory than bed rest and analgesics because it relaxes the muscle spasm.
This highly specific effect, producing relaxation only at the site of demand, is the result of a central action. Norflex is indicated in fibrositis, strains and sprains, acute torticollis, prolapsed intervertebral disc, back pain associated with muscle spasm and other painful muscular conditions.
Each long-acting Norflex tablet contains 100 mg. orphenadrine citrate. In bottles of 100 and 500 tablets. Basic NHS cost: 20/8d. and 93/-.

long-acting Norflex

a single tablet twice a day

relaxes only the muscle in spasm

RIKER

Riker Laboratories Limited

Loughborough, Leicestershire

'Norflex' is a trade mark

RK107

When high-potency Vitamin **B** is indicated . . .

PARENTROVITE and **OROVITE**

Parentrovite — massive dose of injectable B complex with C
for restoring consciousness and rational behaviour in toxic states due to drugs and infective agents . . .
and Orovite — high dosage vitamin B complex for oral use —
for rapid restoration of glucose metabolism.

Standard Reference Cards
Factual information on all our products is available. Produced in accordance with A.B.P.I. Specifications, cards can be obtained from our representatives or from Vitamins Ltd.

VITAMINS LIMITED
Upper Mall, London, W.6.

Proceedings of the Royal Society of Medicine

Vol. 53 177

Section of Experimental Medicine and Therapeutics

President—Professor W. D. M. PATON, D.M., F.R.S.

Meeting
November 10, 1959

THE MEASUREMENT OF BLOOD GAS TENSIONS

Measurement of Blood Oxygen Tension

By J. M. BISHOP, M.D., M.R.C.P.

Birmingham

THE measurement of the blood oxygen tension is not as simple as the measurement of oxygen content but improved techniques are now available and one such method will be described after a review of earlier methods.

The measurement of blood oxygen tension was first achieved by methods based upon the aerotonometer, in which a small bubble of gas is equilibrated with a large volume of blood, and the gas bubble subsequently analysed for oxygen. Krogh (1908) designed a micro-aerotonometer in which blood flowed from a cannulated artery around a bubble which was subsequently drawn into a capillary tube and analysed for oxygen. Barcroft and Nagahashi (1921) devised a method which was similar in principle but, being suitable for analysis of a blood sample contained in a syringe, it was the first method applicable to human experiments. Twenty years later Comroe and Dripps (1944) published a modification of this method and established its accuracy. Then Riley *et al.* (1945) described their use of the Roughton-Scholander syringe for the equilibration of blood with a bubble of gas and for its subsequent analysis. The essential advance was that the whole procedure was carried out in the same syringe. This method has proved of great value in physiological studies but has some disadvantages. It is not for occasional use and requires constant practice, considerable skill and perfect attention to detail. An experimenter may attain repeatability of results and yet show systematic errors, so that it is essential that each individual should assess his own personal accuracy by means of a series of tonometer experiments. The method is most accurate in the range of pO_2 between 40–100 mm Hg and is unsuitable for values above 100 mm Hg, which for many purposes is a serious limitation.

The methods using the principle of the aerotonometer, especially the earlier ones, were not easy to use and in consequence many workers at this time resorted to the highly inaccurate indirect method in which oxygen saturation was measured and the oxygen tension read from a standard oxygen dissociation curve—an inaccurate procedure in the range of values found in arterial blood, because of the shape of the dissociation curve.

When the oxygen tension exceeds 100 mm Hg, it cannot be estimated by any of these methods and it has been measured by determining the oxygen content of anaerobically separated plasma by the manometric method of Van Slyke, or one of several modifications designed to give greater accuracy (Berggren, 1942; Fasciolo and Chiodi, 1946). From a knowledge of the Bunsen solubility coefficient the oxygen tension may then be calculated. With the modifications described, oxygen content can be estimated to about 2% of the measured value, but the method is time-consuming and large errors are introduced by small degrees of hæmolysis.

None of these methods was entirely satisfactory and attention has been directed to a polarographic method, based on the principle evolved by Heyrovsky (1941) using a dropping mercury electrode. The method was first used for blood oxygen tension measurements by Baumberger (1938), and was further developed by Berggren (1942). In essence the method consists of measuring the current flowing in an electrolytic cell to which a potential has been applied, the current being proportional to the quantity of oxygen reduced at the cathode. As the applied potential becomes more negative, the current increases until a plateau is reached at which the current becomes limited by the rate of diffusion of oxygen to the cathode. The chief disadvantage of this type of electrode is that it is unsuitable

for whole blood, measurements having to be made on anaerobically separated plasma. Changes in drop size and variations in other constituents of the plasma result in unpredictable variations in readings, although Bartels (1951) by the use of the potentiometric method overcame some of these objections.

Similar observations were subsequently made using stationary electrodes, usually of platinum. The principles underlying this method are similar and were studied by Kolthoff and his colleagues (Kolthoff and Lingane, 1946). The method was first applied in physiological measurements by Davies and Brink (1942). When blood is in contact with a bare platinum electrode, the rate of reduction of oxygen, and hence the current, changes in time in a manner not fully understood, although it appears to be due largely to the presence of red cells in contact with the electrode. The rate of reduction of oxygen at the platinum surface is then determined by the rate at which oxygen is liberated from combination with hæmoglobin molecules within the red cells in contact with the platinum and the electrode is also sensitive to changes in pH and carbon dioxide tension. Attempts to minimize these effects have followed three principles. First, the electrode may be covered in order to separate it from the blood. Secondly, the potential is applied discontinuously to the cathode and for a short time so that significant oxygen tension gradients within the blood do not develop. Finally the blood may be stirred or otherwise kept in motion relative to the electrode. This also reduces the oxygen tension gradients which develop within the blood as in the case of the dropping mercury electrode. Several workers have combined two or more of these principles in their attempts to measure whole blood oxygen tension. Davies and Brink (1942) used a recessed platinum electrode, the recess being filled with agar, and observed the current ten seconds after applying the potential. They also reported briefly on a cellophane-covered electrode. Olson *et al.* (1949), using cell suspensions but not blood, tried to overcome these difficulties by applying the potential as short pulses and recording the current transients. Morgan and Nahas (1950) used a rotating platinum electrode covered with a film of silicone but failed to eliminate sensitivity to changes in carbon dioxide tension and other unexplained variations. Drenckhahn (1956) used an electrode covered with collodion and reported that it was not influenced by changes of carbon dioxide tension within the physiological range. Clark *et al.* (1953) covered the platinum electrode with a cellophane membrane and reported encouraging preliminary results. Mochizuki and Bartels (1955) used the switched potential method and an uncovered electrode consisting of many platinum points and the blood was not stirred. Oxygen tensions up to 400 mm Hg could be measured but the instrument was still sensitive to changes in hæmoglobin concentration and to some extent to changes in carbon dioxide tension.

The proposal by Clark (1956) that the electrode and reference anode should be incorporated in a cell and isolated electrically from the blood by a membrane permeable to oxygen but not permeable to water or ions was a major advance. It made possible the construction of an instrument which is stable over long periods of time and uninfluenced by other constituents of the blood. Such an instrument is also capable of measuring the oxygen tension of a gas mixture as well as in a liquid phase. Methods for measuring blood oxygen tension using such an electrode have been described by Sproule *et al.* (1957), Kreuzer *et al.* (1958), Severinghaus and Bradley (1958), and by Polgar and Forster (1959). These methods have differed in the manner in which the instrument has been calibrated and the way in which blood has been brought into contact with the electrode.

During the past two years, a convenient and reliable apparatus has been developed and we have reported briefly upon an earlier form of the instrument (Bishop and Pincock, 1958). There are several variables which must be taken into account and these will be briefly discussed before describing the apparatus.

(*a*) *Temperature sensitivity.*—The current output of the electrode rises by approximately 5% per degree centigrade rise in temperature. This effect is due in about equal proportions to the effect of temperature on the platinum cathode and to the effect on the diffusivity of the membrane. Accurate temperature regulation of the electrode system is therefore essential.

(*b*) *Pressure sensitivity.*—The output of the electrode is very sensitive to negative pressure transients, presumably due to displacement of the membrane. Sustained pressure alterations produce less effect but are important under some conditions. These effects can be minimized by correct design of the electrode tip and by firm application of the membrane.

(*c*) *Flow sensitivity.*—When blood or any other liquid at a given oxygen tension is in contact with the membrane of the electrode, the output of the electrode is less than if a gas mixture with the same oxygen tension were substituted. This is due to the fact that the electrode consumes a small quantity of oxygen and oxygen has there-

fore to diffuse through the liquid to reach the membrane, the oxygen tension at the membrane surface being below that in the body of the liquid. The magnitude of this difference can be reduced in two ways, the first of which is the use of a membrane of relatively low diffusibility. The second way is to stir the liquid, when it is found that with increasing rates of movement the difference between gas and liquid readings diminishes, but does not disappear altogether because a boundary layer of stationary fluid always remains. Furthermore, when water and blood of the same oxygen tension are compared, the greater viscosity of blood results in a thicker boundary layer and hence the electrode output is always lower than for water, although the difference is proportionately constant. This is important when calibrating because a correction must be applied if water is used for this purpose.

(*d*) *Response time.*—This is very largely dependent on the diffusibility of the membrane which may be varied by changing the thickness or the material used. Although very small cathodes have been reported to give a fast response time, this has not been related to platinum area within the range studied.

Thus several features in the design require a compromise. The apparatus illustrated in Figs. 1 and 2 has been evolved through a series of modifications. Details of the construction show the electrode held in a stainless steel block, a recess in which, covered by a glass plate, forms the chamber, 1 ml in volume, into which blood is introduced. Water circulates through the Perspex water jacket from a temperature-regulated water bath, which is maintained at $38° \pm 0{\cdot}1°$ C. The electrode tip has a taper which permits the membrane to be applied firmly and held in place by a rubber O-ring. The membrane is of polyethylene 0·125 mm thick. The blood is stirred magnetically at a speed of 2,000 rev/min by a glass-coated soft iron slug, the dimensions of which are such that the clearance between it

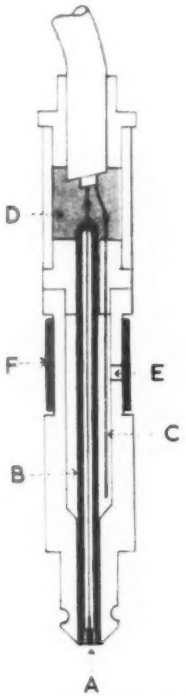


FIG. 1.—Details of electrode construction. The body of the instrument is made of Perspex. A, platinum cathode fused in glass (B). C, silver-silver chloride anode. D, epoxy resin cast around electrode connections to cable. E, hole for introduction of electrolyte and covered by rubber diaphragm (F).

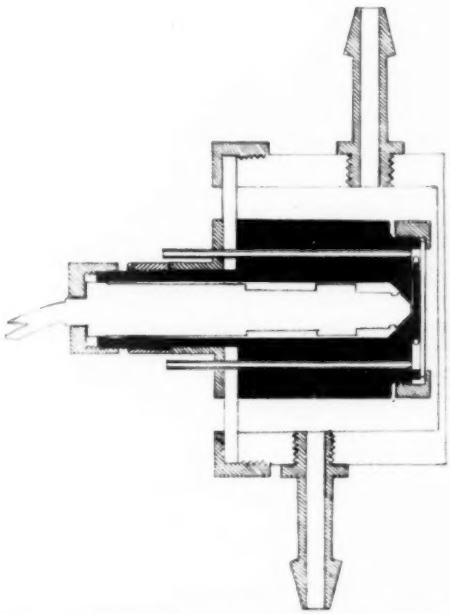


FIG. 2.—Section through the assembled instrument. The electrode is in place in the stainless steel block (solid black) which is surrounded by a water jacket. The recessed measuring chamber is shown with its glass cover and contained stirring slug.

and the membrane is 0·05 mm. The voltage-current relationship for such an electrode shows a plateau between −0·4 and −0·7 volt. In use, a potential of −0·6 volt is applied to the electrode and the current resulting flows through a variable series resistance. The potential drop across this resistance is measured by means of an electrometer (E.I.L. 33B Vibron electrometer) and recorded by an Elliott recorder. The time response of the electrode is not exponential, there being a prolonged "tail". In practice the response is complete in four minutes, this also allowing for the blood to assume the temperature of the water jacket. Calibration is by means of water equilibrated with gas mixtures at two levels of oxygen tension by bubbling in suitable vessels held in the water bath. Water is transferred to the electrode chamber by siphonage through nylon tubes.

The current output is linearly related to oxygen pressure from zero to one atmosphere. To assess the overall accuracy of the method specimens of blood and of water have been prepared in a double tonometer rotating in a water bath from which the water perfusing the water jacket of the apparatus was drawn. The blood was equilibrated by continuously passing a gas mixture of known composition through the tonometer for 25 minutes. Both blood and water were in turn siphoned into the chamber and the oxygen tension estimated in duplicate in the usual manner. Thirty-seven pairs of estimations were made and in the case of water the points were distributed about the line of identity. In the case of blood this was not so, the estimated value always falling below the tonometer value. The relationship between the tonometer and estimated values was constant and a linear regression line was calculated. The precision of the method was satisfactory and in the range 0–150 mm Hg the standard deviation about the regression line was 2·1 mm Hg. Some of this error is related to the preparation of the blood in the tonometer and its transfer to the measuring instrument, so that the error of the measurement has probably been overestimated.

By the use of this instrument we have a versatile method which is suitable for the measurement of the oxygen tension in blood, and incidentally in other fluids, and also in gas mixtures. It is accurate and will measure oxygen tension from zero to one atmosphere of oxygen. It is simple to use and gives results quickly; ten samples can be analysed in one hour. The instrument has been in use in physiological studies during the past year and continues to work satisfactorily.

REFERENCES

BARCROFT, J., and NAGAHASHI, M. (1921) *J. Physiol.*, **55,** 339.

BARTELS, H. (1951) *Pflüg. Arch. ges. Physiol.*, **254,** 107.

BAUMBERGER, J. P. (1938) *Amer. J. Physiol.*, **123,** 10.

BERGGREN, S. M. (1942) *Acta physiol. scand.*, **4,** Suppl. 11.

BISHOP, J. M., and PINCOCK, A. C. (1958) *J. Physiol.*, **145,** 20P.

CLARK, L. C. (1956) *Trans. Amer. Soc. Art. Int. Org.* **2,** 41.

——, WOLF, R., GRANGER, D., and TAYLOR, Z. (1953) *J. appl. Physiol.*, **6,** 189.

COMROE, J. H., and DRIPPS, R. D. (1944) *Amer. J. Physiol.*, **142,** 700.

DAVIES, P. W., and BRINK, F. (1942) *Rev. sci. Instrum.* **13,** 524.

DRENCKHAHN, F. O. (1956) *Pflüg. Arch. ges. Physiol.*, **262,** 169

FASCIOLO, J. C., and CHIODI, H. (1946) *Amer. J. Physiol.*, **147,** 54.

HEYROVSKY, J. (1941) Polarographie. Vienna.

KOLTHOFF, I. M., and LINGANE, J. J. (1946) Polarography. New York.

KROGH, A. (1908) *Skand. Arch. Physiol.*, **20,** 259.

KREUZER, F., WATSON, T. R., Jr., and BALL, J. M. (1958) *J. appl. Physiol.*, **12,** 65.

MOCHIZUKI, M., and BARTELS, H. (1955) *Pflüg. Arch. ges. Physiol.*, **261,** 152.

MORGAN, E. H., and NAHAS, G. G. (1950) *Amer. J. Physiol.*, **163,** 736.

OLSON, R. A., BRACKETT, F. S., and CRICKARD, R. G. (1949) *J. gen. Physiol.*, **32,** 681.

POLGAR, G., and FORSTER, R. E. (1959) *Fed. Proc.*, **18,** 433.

RILEY, R. L., PROEMMEL, D. D., and FRANKE, R. E. (1945) *J. biol. Chem.*, **161,** 621.

SEVERINGHAUS, J. W., and BRADLEY, A. F. (1958) *J. appl. Physiol.*, **13,** 515.

SPROULE, B. J., MILLER, W. F., CUSHING, J. E., and CHAPMAN, C. B. (1957) *J. appl. Physiol.*, **11,** 365.

Measurement of Blood Carbon Dioxide Tension

By J. F. NUNN, Ph.D., F.F.A.R.C.S.

London

IN the gas phase, tension is synonymous with partial pressure, which is defined by Dalton's law as the pressure a gas would exert if it occupied the volume alone. The tension of a gas in a liquid is a concept more familiar to the biologist than the physicist. Krogh (1908) has defined it as the partial pressure of the gas in an atmosphere which is in diffusion equilibrium with the liquid. This is, in fact, the basis of many of the methods of measurement of carbon dioxide tension (pCO_2) of blood.

There are at least three reasons for measuring carbon dioxide tension in preference to content. Firstly, the tissues of the body are sensitive to

the tension of carbon dioxide in the blood which perfuses them. The respiratory centre, for example, will respond to an increase in carbon dioxide tension without an accompanying increase in content, but it will not respond to an increase in content alone. Secondly, the tension provides a link between the gas and liquid phases of the body. Thus end-pulmonary capillary blood has the same pCO_2 as the alveolar gas. Finally, Bohr's equation can express the balance of carbon dioxide production and elimination in the form of the arterial pCO_2. Therefore, from both the clinical and academic points of view, measurement of tension is generally more rewarding.

The arterial pCO_2 may be derived indirectly from the study of alveolar or end-tidal gas, and of mixed venous or "arterialized" venous blood. This paper, however, is concerned solely with methods based on arterial puncture. There is little difficulty in sampling arterial blood under anaerobic conditions, and thereafter the blood is best stored in the syringe into which it is taken. There is no evidence that carbon dioxide is lost from a well-fitting lubricated syringe which has been capped. Nevertheless, changes occur in the blood if it is allowed to remain at or above room temperature, e.g. a slow fall in CO_2 content and a rapid fall in pH, which cannot easily be prevented with fluoride (Nunn, 1959), and results in an appreciable rise of pCO_2 as has been directly confirmed by Hobsley (1959). It is difficult to say whether these changes are largely respiratory or metabolic but whatever the cause, the pCO_2 of shed blood rises about 0·1 mm Hg per minute when stored at room temperature. It is thus necessary to carry out the analytic procedures immediately or to store the blood on ice if this is not practicable.

pH and pCO_2 change not only with time but with temperature. It is therefore important to correct for the difference between the body temperature of the patient and the temperature at which the measurements are made (Bradley *et al.*, 1956). This correction is too large and too variable to use if the two temperatures differ by more than a few degrees. pH and pCO_2 should therefore be measured near 37° C unless the patient is hypothermic.

Equilibration Methods

The techniques for measurement of pCO_2 fall into four groups. The first, the equilibration method, is based directly upon the definition of Krogh. A small bubble of gas is brought into equilibrium with a larger volume of blood. The bubble is then analysed for carbon dioxide and the pCO_2 derived from fractional concentration and barometric pressure. This technique was first used in 1872 by Pflüger (Strassburg, 1872), and later developed amongst others by Krogh (1908).

A major advance occurred in 1921 when Barcroft and Nagahashi equilibrated 0·1 ml of alveolar gas with 10 ml of arterial blood. This enabled the technique to be used in man and was the forerunner of "bubble tonometry" (Riley *et al.*, 1957). This technique yields both pCO_2 and pO_2 and has been directly responsible for many of the major advances in knowledge of respiratory function over the last few years. It is no less valuable in the management of patients with respiratory disease.

The method requires little apparatus although it demands skill and practice of the operator. A duplicate analysis can be carried out in 30 minutes and the standard deviation of the pCO_2 is 1·7 mm Hg in expert hands. Unfortunately the method cannot be used in patients anæsthetized with nitrous oxide.

Indirect Method

For many years the only practicable alternative to equilibration techniques has been the indirect method based upon the following form of the Henderson-Hasselbalch equation:

$$pCO_2 = \frac{\text{plasma } CO_2 \text{ content}}{S\ (\text{antilog}\ (pH - pK') + 1)}$$

where S is the solubility factor for CO_2. The accuracy of this method depends upon our ability to ascribe values to the factors on the right hand side of the equation.

The plasma CO_2 content is usually determined with the Van Slyke-Neill manometric apparatus and presents little problem. A small modification is required if anæsthetic gases are present in the blood of the patients. The analysis is not critical as an error of 0·2 mEq/l. corresponds to only 1% of the value for pCO_2.

The solubility factor for CO_2 (S) is commonly assumed to be 0·0301 mEq/l. at 38° C. It is unlikely that this is a serious source of error.

The measurement of pH is the most critical part of the method. An error of 0·01 unit is easily made and this will alter the pCO_2 by 2·5%. Severinghaus and his co-workers (1956*a*) have reviewed the errors in the measurement of pH but it may, perhaps, be stressed that a meter is required which will measure pH with a standard deviation of less than 0·005 unit and rigorous temperature control is essential.

The value assumed for pK′ is no less important than the measurement of pH, since here too, an error of 0·01 will affect the pCO_2 by 2·5%. pK′

varies with temperature and pH (Severinghaus *et al.*, 1956*b*). Many of the buffer standards in current use are not mutually compatible and the value used for pK′ should take this factor into account.

Using the indirect method, Severinghaus has measured pCO_2 with a standard deviation of 0·3 mm Hg. Thornton and Nunn (1960) have been content with a figure of 1·1 mm Hg. The method is cumbersome, requiring a good pH meter, a Van Slyke apparatus and facilities for anaerobic centrifuging. Nevertheless, where these techniques are already available, indirect measurement of pCO_2 may be established with no great trouble, and is probably still the method of choice.

Interpolation Methods

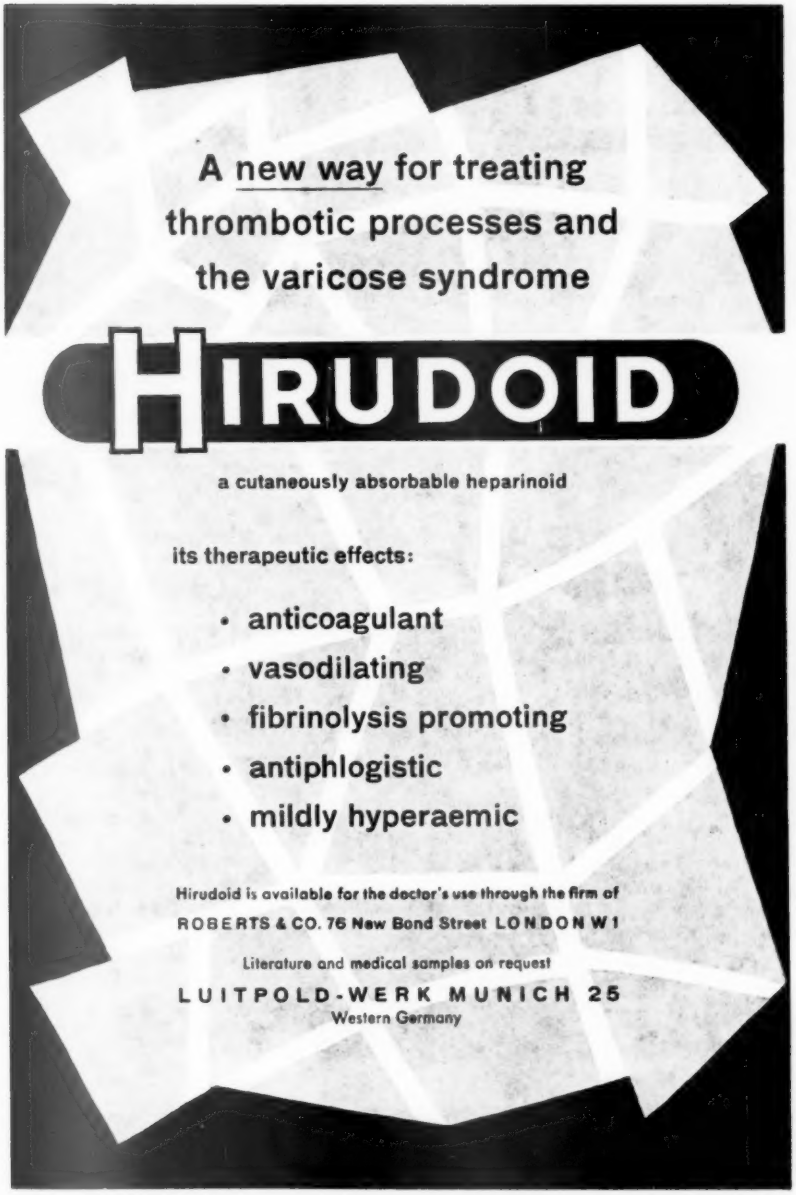
The interpolation methods are based on a graph of pCO_2 against either CO_2 content or pH. Interpolation of these quantities will then yield the pCO_2. This method was first used with a CO_2 dissociation curve but is now generally used with a pH/log pCO_2 plot. This has the advantage of being straight and so may be defined by only two equilibrations. The only measurement required is the pH and, in effect, the pCO_2 of the blood is compared with the pCO_2 of the gas mixtures used for equilibration. Thus only the pH difference is required and this may be measured with considerable accuracy since most of the sources of error in the measurement of absolute pH are by-passed. Astrup (1956, 1959) has introduced ingenious devices which have made the interpolation method rival the indirect for simplicity. Either plasma or blood may be used. In the case of plasma there is, however, considerable difficulty in separating the plasma without changing the pCO_2 (Nunn, 1959). In the case of blood, a small error is introduced if the initial sample is desaturated (Astrup, 1959). Nevertheless, the results are comparable with other methods of measurement of pCO_2 and a standard deviation of 1·2 mm Hg is possible (Nunn, 1959). The method is quite unaffected by the presence of anæsthetic gases.

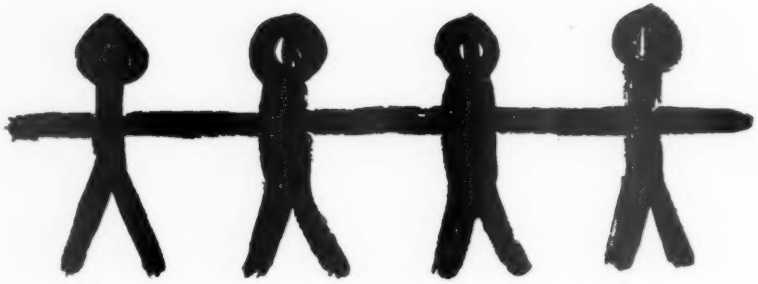
Titration Method

The latest approach to the measurement of pCO_2 consists of a titration of CO_2 against a standard sodium hydroxide solution. Molecular CO_2 concentration is proportional to pCO_2, and the magnitude of the change in the bicarbonate may be conveniently measured by the change in pH. Fortunately thin plastic membranes are permeable to molecular CO_2 but not to charged ions. Therefore if blood (or gas) is separated from a standard bicarbonate solution by a thin membrane, the pH change in the bicarbonate solution is inversely proportional to the log of the pCO_2 of the sample. Severinghaus (1959) has described an electrode assembly which is compact and has a response time of under a minute. Less than 1 ml of blood is required. Since the response to blood and gas is the same, calibration can be very simply carried out with a known mixture of CO_2 in oxygen. It is of interest that with this method the optimum sensitivity is still 0·01 pH unit for a 2·5% change in pCO_2. However, the method should prove more accurate by virtue of its greater simplicity

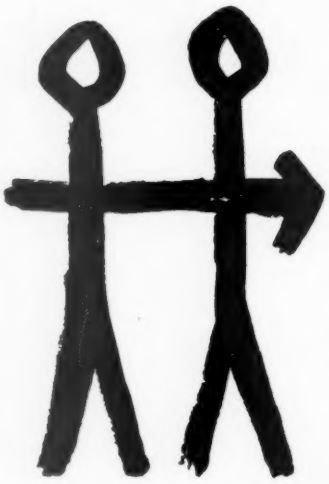
REFERENCES

ASTRUP, P. (1956) *Scand. J. clin. Lab. Invest.*, **8**, 33.
—— (1959) In: Symposium on pH and blood gas measurement. Edited by R. F. Woolmer. London; p. 81.
BARCROFT, J., and NAGAHASHI, M. (1921) *J. Physiol.*, **55**, 339.
BRADLEY, A. F., STUPFEL, M., and SEVERINGHAUS, J. W. (1956) *J. appl. Physiol.*, **9**, 201.
HOBSLEY, M. (1959) Personal communication.
KROGH, A. (1908) *Skand. Arch. Physiol.*, **20**, 259.
NUNN, J. F. (1959) In: Symposium on pH and blood gas measurement. Edited by R. F. Woolmer. London; p. 60.
RILEY R. L., CAMPBELL, E. J. M., and SHEPARD, R. H. (1957) *J. appl. Physiol.*, **11**, 245.
SEVERINGHAUS, J. W. (1959) In: Symposium on pH and blood gas measurement. Edited by R. F. Woolmer. London; p. 126.
——, STUPFEL, M., and BRADLEY, A. F. (1956*a*) *J. appl. Physiol.*, **11**, 189.
——, ——, —— (1956*b*) *J. appl. Physiol.*, **11**, 197.
STRASSBURG, G. (1872) *Pflüg. Arch. ges. Physiol.*, **6**, 65.
THORNTON, J. A., and NUNN, J. F. (1960). In preparation.


A new way for treating
thrombotic processes and
the varicose syndrome
HIRUDOID
a cutaneously absorbable heparinoid
its therapeutic effects:
• anticoagulant
• vasodilating
• fibrinolysis promoting
• antiphlogistic
• mildly hyperaemic
Hirudoid is available for the doctor's use through the firm of
ROBERTS & CO. 76 New Bond Street LONDON W1
Literature and medical samples on request
LUITPOLD-WERK MUNICH 25
Western Germany



10 unknown diabetics in every GP's care...



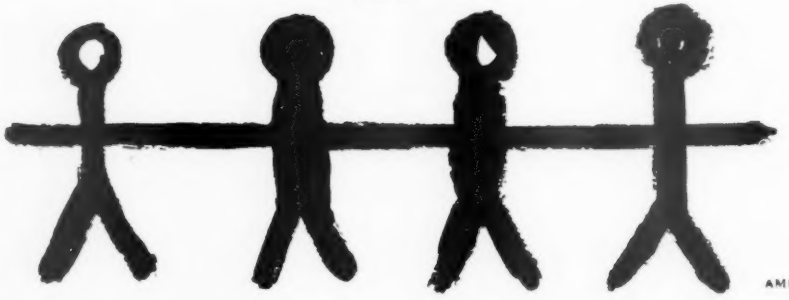
The diabetic population of Great Britain numbers almost 500,000—yet only about half of them are known and under treatment. Statistically this means that every general practitioner has more than ten undetected diabetics in his care.
These unknown diabetics are at risk. Many already show retinal changes and other vascular abnormalities at the time of diagnosis. These changes are often irreversible: their prognosis could only be improved by early diagnosis and treatment of diabetes.
CLINISTIX* is the best aid to the diagnosis of diabetes. This simple dip-and-read test is specific for glucose: it takes only a few seconds, and has the correct sensitivity for significant results. Every patient whose urine is positive to CLINISTIX should be regarded as a potential diabetic.

to detect diabetes simply dip-and-read Clinistix

CLINISTIX Reagent Strips are available in bottles of 60 strips. U.K. Retail Price 6/-, less professional discount. From all chemists

Ames Company *Division of Miles Laboratories*
Nuffield House Piccadilly London W1

*Trade Mark



AM144

Section of Anæsthetics

President—J. ALFRED LEE, F.F.A. R.C.S., D.A.

Meeting
December 4, 1959

Anæsthesia in Dystrophia Myotonica [*Abridged*]

A Review of the Hazards of Anæsthesia

REGISTRAR'S PRIZE ESSAY

By LEON KAUFMAN, M.B., F.F.A. R.C.S.
London

RECENT comments on the use of thiopentone in patients suffering from dystrophia myotonica have assessed this drug unfavourably, small doses apparently producing prolonged respiratory depression (Dundee, 1952; Bourke and Zuck, 1957; Lodge, 1958; Pachomov and Caughey, 1958). It has been postulated that as the disease is a myopathy, this singular response must be peripheral and that thiopentone exerts its action on muscle itself (Dundee, 1952).

A series of case reports of patients suffering from dystrophia myotonica has recently been studied, and careful scrutiny has in many instances failed to confirm this respiratory depressant effect of thiopentone. On the other hand, in patients who have died in the immediate post-operative period, ether and morphine have been implicated, and two cases of sudden death in this disease are recorded in which neither anæsthesia nor surgery was involved (Spillane, 1951; Fisch and Evans, 1954).

In view of these diverse findings, it became necessary to reconsider the nature of the disease in detail and to reassess the impact of anæsthesia on it.

Case records of over 100 patients suffering from dystrophia myotonica collected by the late Dr. O. Maas before 1939 were inspected and 10 were found to have had operations. One patient died in the immediate post-operative period but no details were available.

In the present series, 79 cases of myotonia have been collected, 8 of myotonia congenita, and 71 of dystrophia myotonica (Table I). Of the cases

TABLE I.—"MYOTONIC SYNDROME"

Total No. of cases	79
Myotonia congenita	8
Operations	2
Dystrophia myotonica	71
No operation	24
(admitted with bronchopneumonia 2)	
Operations (no details)	7
Operations	25
Cataract extractions (local analgesia)	15

of dystrophia myotonica, 30 had been given oral barbiturates and no abnormal response was noted, but neither respiratory depression nor prolonged sleep was specifically observed and may have in fact occurred. 15 had cataract extractions under local analgesia without incident. 24 patients did not undergo surgical treatment, but of these 2 were admitted with bronchopneumonia. 32 were submitted to operation but full details are available only in 25 cases. Of these 25 patients 5 had respiratory depression or prolonged apnœa, and a further 4 died (Table II).

TABLE II.—25 OPERATION CASES

I Uneventful	15
II Myotonia	1
III Respiratory complications	5
IV Mortality	4

Dystrophia myotonica is portrayed as a generalized disease with implications of consequence for the anæsthetist, for insufficiency of many a bodily system may be associated with it. Muscular atrophy of a widespread nature and diffuse weakness are not uncommon, affecting not only the sternomastoids, the most important accessory muscles of inspiration (Campbell, 1958), but also the intercostals, the diaphragm, the abdominal musculature, and the larynx. Sternomastoid wasting resulting in inability to raise the head may lead to respiratory obstruction especially in the post-operative period while, consequent upon atrophy, the larynx may lose its protective function. In addition, ventilation may be impaired by myotonia affecting the muscles of respiration. Unilateral elevation of the diaphragm when present is considered not to be due to atrophy or myotonia but a congenital varient of the disease (Caughey and Gray, 1953; Caughey, 1954). The heart is often affected, and defects of conduction and rhythm are frequently present. Adrenocortical function appears impaired to some extent; metabolic rate is depressed; and patients treated with cortisone for myotonia may, unless the dose is adjusted for the stress of operation, become exposed to yet a further hazard. A further complication of steroid therapy especially with triamcinolone and pred-

nisone is that, though they may be of value in the treatment of the myotonia, they themselves can cause muscle wasting: EMG changes are characteristic of a myopathy.

The earliest description of risk associated with anæsthesia is that of a case of myotonia congenita (Johnson and Marshall, 1915). Dyspnœa was present pre-operatively, and at the operation for muscle biopsy, when open ether was administered, respiration was irregular, cyanosis was persistent, and general muscular spasm troublesome. The patient remained semi-stuporous for twenty-four hours.

No more mention was made of the disease in anæsthesia until Dundee (1952), Hewer (1957) and Lodge (1958) recorded cases of apnœa lasting up to 20 minutes and respiratory depression for up to 40 minutes, after only 100 mg thiopentone. However, the import of these observations is lessened by the fact that premedication in the form of pethidine and morphine may have contributed to the respiratory depression. Similarly, the multiplicity of drugs administered in the cases reported by Bourke and Zuck (1957) and Pachomov and Caughey (1958) detracts from the suspicion that thiopentone was the miscreant. In the former, papaveretum, scopolamine, thiopentone, succinylcholine, pethidine, and lignocaine (in spray form) were employed, producing prolonged apnœa. In the latter, quinalbarbitone, thiopentone, ethyl chloride and ether were administered; death occurred half an hour after cessation of the operation, respiration apparently "becoming arrested", and might well have been attended by respiratory obstruction.

Some of the patients so described resemble those suffering from a relative overdose of central respiratory depressant drugs. To produce central depression may require large doses of drugs in the fit patient, but very much less is necessary in the dystrophic one, with wasted muscles of respiration. The dystrophic process may affect the larynx, facilitating intubation, while the low metabolic rate may prolong the action of the drugs as the rate of detoxication is reduced.

Failure of inhalation of carbon dioxide to stimulate respiration during apnœa has suggested to Dundee (1952) that the action of thiopentone was not central; however, the carbon dioxide tension in the blood may already have been elevated. His experiment of giving 50 mg of thiopentone to a single volunteer, which produced respiratory depression without loss of consciousness, is not absolute evidence of a peripheral effect of the drug; it is beset by difficulty in interpretation in the face of the complicated chemical and nervous mechanisms of breathing. That thiopentone has an action on peripheral nerve and the neuromuscular junction in the experimental animal (Secher, 1951; Kraatz and Gluckman, 1954; Sirnes, 1954; Quilliam, 1955) has been shown, but in high concentrations, while lower doses are more effective centrally (Goodman and Gilman, 1955).

Thus an assessment of the cases recorded in the literature of the last decade does not endorse the suggestion that the action of thiopentone is upon abnormally sensitive muscle, but suggests that muscle wasting with reduced pulmonary ventilation leads to increased arterial pCO_2 and is further accentuated by respiratory depressants such as morphine, pethidine and thiopentone.

In the present study in patients suffering from dystrophia myotonica, response to general anæsthesia has been quite uneventful in many cases (Table III), one patient having 500 mg of thiopentone on three occasions within one week without apparent ill-effect. The presumption is thus fostered that it is not the thiopentone *per se* which produces a specific idiosyncrasy in this disease as it does in acute intermittent porphyria. It may well be that the state of disease was not extensive in Group I (Table III), or that the doses of drugs administered were commensurate with the general physical health of the patients.

TABLE III

GROUP I.—Anæsthesia uneventful—15 cases

A. Local and spinal analgesia
- (*a*) Submucous resection 1
- (*b*) Thoracoplasty 2
- (*c*) Hæmorrhoidectomy 1

B. General anæsthesia
- (*a*) Biopsy ... ... 4 (no thiopentone in 3 cases)
- (*b*) Myomectomy (thiopentone, gallamine)
- (*c*) Cholecystectomy (succinylcholine, tubarine, neostigmine)
- (*d*) Inguinal hernia (thiopentone, gallamine)
- (*e*) Thyroidectomy (N_2O-O_2 ether) → Termination of pregnancy (thiopentone 500 mg, N_2O-O_2, ether—on three occasions)
- (*f*) Dental extraction (N_2O-O_2)
- (*g*) Mastoidectomy (thiopentone, gallamine, N_2O-O_2, ether)
- (*h*) Examination under anæsthesia, dilatation and curettage (thiopentone, N_2O-O_2, trichlorethylene)

One patient (Group II) developed myotonia of the hands in response to incision on both the occasions she was anæsthetized (Table IV). This resolved as the operations progressed: myotonia of the respiratory muscles was not observed.

TABLE IV

GROUP II.—*Myotonia*—1 case
- Papilloma of breast (thiopentone 150 mg, N_2O-O_2)
- Axillary abscess (thiopentone 250 mg, N_2O-O_2)

GROUP III.—*Respiratory Complications*—5 cases
- (*a*) Cataract (thiopentone, gallamine, N_2O-O_2)
- (*b*) Hernia (thiopentone, pethidine, N_2O-O_2)
- (*c*) Gastro-enterostomy (thiopentone, tubarine, C_2H_4, O_2)
- (*d*) Resection of urethral bar (thiopentone 200 mg, N_2O-O_2, trichlorethylene)
- (*e*) Dental extractions (thiopentone, succinylcholine, N_2O-O_2)

GROUP IV.—*Mortality*—4 cases
- (*a*) Polycystic kidneys; blood urea 300 mg (thiopentone 500 mg, hypothermia)
- (*b*) Cæsarean section (buthalitone, intermittent succinylcholine)
- (*c*) Gastrectomy (thiopentone, succinylcholine, tubarine)
- (*d*) Cholecystectomy (N_2O-O_2, ether)

Laryngoscopy was performed with ease at the end of the operation. This patient had absent sternomastoids, was unable to raise her head, and had diaphragmatic respiration prior to anæsthesia. Subsequent lung function tests confirmed her respiratory inadequacy, with a maximum breathing capacity of 56 litres/minute, and maximum expiratory pressure of 10 mm Hg (H. N. in Table V).

The patients in Group III (Table IV) represent instances where in the presence of poor physical condition and diminished respiratory reserve the action of respiratory depressant drugs was enhanced. All the patients had morphine premedication followed by 250–500 mg thiopentone, and one also had 25 mg pethidine during anæsthesia. Respiratory depression lasting 30 minutes ensued in one instance (hernia repair), while apnœa lasting 30 minutes (cataract extraction) and four hours (gastro-enterostomy) occurred in 2 other cases: all responded to nikethamide.

The patient undergoing resection of urethral bar had marked wasting of all his muscles (he weighed 8 st. 7 lb), diminished vital capacity and auricular flutter. It is hardly surprising that after papaveretum 20 mg and scopolamine 0·4 mg only 200 mg thiopentone and nitrous oxide, oxygen and trichlorethylene were necessary to maintain adequate anæsthesia. Laryngoscopy was performed with ease at the end of the operation. The patient was returned to the ward conscious but had a short period of cyanosis while lying on his back, presumably due to respiratory obstruction.

The child having dental treatment had absence of sternomastoids and wasting of the abdominal muscles. His weight was 3 st. 11 lb. Premedication consisted of papaveretum 16 mg, scopolamine 0·3 mg. After 125 mg thiopentone apnœa ensued lasting for 2 minutes and was terminated by gentle stimulation. Succinylcholine (30 mg) produced myotonia of the hands for one minute. At no time was there any suggestion of myotonia of the respiratory muscles. Spontaneous respiration did not recommence until the end of operation, the patient being manually ventilated with nitrous oxide and oxygen via a nasotracheal tube. Breathing began with movement of the tube *in situ*, respiration being slow and deep.

The patients who died under anæsthesia (Group IV) were all markedly debilitated. A patient undergoing gastrectomy recovered satisfactorily from anæsthesia, only to succumb in the post-operative period after the administration of 20 mg of papaveretum, while another having a cholecystectomy under nitrous oxide, oxygen and ether anæsthesia died suddenly five hours post-operatively, no specific cause being found at post-mortem.

The patient with polycystic kidneys and progressive renal failure (blood urea 300 mg) had multiple punctures performed of the renal cysts under hypothermia, which did not appear to have induced an attack of myotonia. The patient died shortly after return to the ward being unable to cough up secretions.

The patient undergoing Cæsarean section had a severe degree of muscle wasting, crepitations at the lung bases and right bundle branch block, all of which increased the risk of operation. Immediate recovery from anæsthesia was satisfactory but shortly afterwards she became cyanosed and had to have artificial respiration. Bronchial secretions became exceedingly profuse and death occurred eight hours post-operatively.

All the patients in the last group had marked lack of respiratory reserve power and succumbed in the immediate post-operative period presumably as a result of under-ventilation, possible respiratory obstruction and the inability to expectorate secretions. There are also to be noted the effects of anoxia, and the depressant action of thiopentone (Prime and Gray, 1952) on the already damaged heart, while ventilation might be further impaired as a result of abdominal operation (Anscombe, 1957).

Respiratory Function in Neurological Disease

Many of the problems created by respiratory weakness and bulbar palsy in poliomyelitis have been largely solved but it is of great interest that of the 39 cases of myasthenia gravis collected by Rowland *et al.* (1956) 14 died within an hour of being sedated.

In a patient aged 34 suffering from amyotrophic lateral sclerosis (Feltman *et al.*, 1952) diaphragmatic excursion was limited, resulting in a decreased vital capacity of 2,285 ml, maximum breathing capacity of 38 litres/minute, increased arterial pCO_2, oxygen unsaturation (73·3% oxygen saturation), and polycythæmia. The patient developed congestive cardiac failure, presumably from the effect of anoxia on the myocardium, and the effect of anoxia and polycythæmia on the pulmonary vascular bed leading to increased resistance. Miller (1957) found the maximum breathing capacity (M.B.C.) of 2 cases of progressive muscular atrophy and one of amyotrophic lateral sclerosis to be reduced to 32, 42 and 57 litres/minute respectively.

Kilburn *et al.* (1959) and Bashour *et al.* (1955) both reported one case each of dystrophia myotonica with reduced vital capacity (V.C.) and M.B.C. Benaim and Worster-Drought (1954) described one case with myotonia of the diaphragm with a vital capacity of 1,130 ml,

M.B.C. of only 45 litres/minute and arterial pCO_2 of 67·4–72·1 mm Hg. In the present investigation of respiratory function in dystrophia myotonica, V.C., forced expiratory volume over 1 second ($F.E.V._1$), M.B.C. and maximum expiratory pressures were all measured. Indirect M.B.C. was calculated from the $F.E.V._1$ by multiplying the result by 35 (Table V). Reduction

TABLE V.—RESPIRATORY STUDIES IN DYSTROPHIA MYOTONICA

	Age	V.C. ml	$F.E.V._1$ ml	$\frac{F.E.V._1}{V.C.}$	Indirect M.B.C. l./min	Direct M.B.C. l./min	Max. exp. pressure mm Hg
J. G.	23	3,700	2,900	83%	105–100	75–80	20
D. H.	39	2,800	2,580	92%	91	72–75	20
H. N.	44	2,200	1,700	82%	65	56	10
G. C.	49	2,500	1,950	78%	68		
C. J.	34	2,900	2,500	80%	95	65	12

of the maximum expiratory pressure to 20 mm Hg or less from the normal of 100 revealed marked weakness of the muscles of expiration. The indirect M.B.C., within the normal range in three instances, was markedly reduced on direct measurement, indicating that sustained voluntary effort was more difficult than a single rapid expiration. Thus if these patients are exposed to the stress of depressant drugs or respiratory infection respiratory failure may easily ensue.

Myotonia

The phenomenon of myotonia has been investigated by Brown and Harvey (1939) who demonstrated, in congenital myotonia of the goat, where the muscles on electromyography are similar to those of human myotonia congenita, that the abnormality is in the muscle fibre itself, and that contraction is due to a long-lasting irregular tetanus. The prolonged discharge of action potentials on direct stimulation of the muscle is unaltered by nerve section or curarization, and hence the neuromuscular junction is not involved. The repetitive response is increased by acetylcholine and potassium ions, but only in concentrations which normally cause some contraction (Denny-Brown and Foley, 1949). Quinine has a depressant action on the excitability of the myoneural junction and also an effect on the muscle fibre itself where it prolongs the refractory period (Harvey, 1939), and it is this latter action that is so beneficial in the treatment of myotonia. The repetitive discharge of impulses can be induced in normal skeletal muscle by veratrine and abolished by quinine. This action appears to be associated with increased potassium leakage from the cells (Krayer and Acheson, 1946). The resting muscle membrane potential is believed to be proportional to the logarithm of the ratio of the potassium within the cells to that outside the cells. Thus an increase of the extracellular potassium will lead to an unstable membrane and depolarization (Grob *et al.*, 1957).

That the defect of myotonia is within muscle and not at the myoneural junction has been confirmed in man using intra-arterial curare (Lanari, 1946; Landau, 1952), while more recently it was noted by Geschwind and Simpson (1955) that 10 mg of *d*-tubocurarine or 15 mg of decamethonium could not abolish myotonia. The defect may well be an inherent intracellular metabolic disorder allowing potassium to escape more easily from the cells.

Anæsthetic Management

Guidance for the anæsthetic management of patients with dystrophia myotonica should be based on prime principles; critical assessment of the severity of the disease, the extent of the dystrophy and the disability arising from the myotonia is imperative. Lung function should be evaluated, with measurements of vital capacity, forced expiratory volume (1 second) and maximum breathing capacity, while fluoroscopy of the chest should be done to see whether myotonia of the diaphragm can be detected. Cardiovascular involvement may be present, and the possibility of endocrine dysfunction, especially adrenocortical, must be considered. Techniques of anæsthesia and the drugs administered are influenced by due consideration of all these factors. Thus, if respiratory reserve power is diminished, respiratory depressants should be avoided, though emotional upset and fright, such as coming to the operating theatre without sedation, may induce an attack of myotonia as indeed does decrease in temperature. If any respiratory infection is present, mortality increases even without anæsthesia, and non-urgent operations are best avoided. Ventilation should at all times be adequate, but if it should prove otherwise, controlled respiration should be resorted to without delay. The patient may require assistance to respiration also in the post-operative period, when secretions cannot be coughed up, and when ventilation as seen by studies of vital capacity, maximum inspiratory and expiratory flow rates is diminished after operation (Anscombe, 1957). Tracheostomy and artificial ventilation may be required. Myotonia of the respiratory muscles may make ventilation extremely difficult if not impossible, and though curare will not be effective, intravenous quinine has been recommended as the drug of choice to relieve the attack, in the dosage of 300–600 mg of the hydrochloride. Spinal analgesia does not abolish myotonia, which is induced by percussion of muscle. Grund (1919) and Kennedy and Wolf (1937) both report one instance each of persistent myotonia after spinal anæsthesia, which may make operating conditions difficult. Likewise, brachial plexus nerve block, which

produced both motor and sensory paralysis, also could not abolish myotonia produced by mechanical stimulation of muscle (Buchtal and Clemmensen, 1941).

Myotonia, being a disorder of muscle, is abolished by infiltration of the muscle with local anæsthesia (Buchtal and Clemmensen, 1941; Landau, 1952) and this appears to be the anæsthetic of choice if myotonia is troublesome, and the technique is suitable for the nature of the operation.

Relaxants of the competitive type are not contra-indicated, but they do not abolish myotonia; dosage would have to be reduced if the patient is taking quinine, which also has a depressant effect at the end plate (Harvey, 1939). Depolarizing relaxant drugs are at present best avoided if myotonia is marked, since a patient receiving decamethonium had an attack of myotonia with respiratory distress (Richardson, 1959) and it is known that, in the experimental animal, succinylcholine can elevate the serum potassium (Paton, 1956) which can aggravate myotonia. Neostigmine was considered to increase myotonia (Kennedy and Wolf, 1937) but in a more recent study (Landau, 1952) no significant change was detected.

This appraisal of anæsthesia and dystrophia myotonica was initiated with the intention of confirming that the action of thiopentone in this disease was a peripheral one on muscle: this view has been dispelled. It has been shown that patients have undergone thiopentone anæsthesia without incident, though the administration of anæsthesia is still fraught with danger, depending on the severity of the disease. It has also been revealed that there is possible cardiac impairment and endocrine dysfunction, while the respiratory insufficiency resulting from dystrophy or myotonia of the respiratory muscles may be accentuated by the presence of respiratory depressant drugs. The suggestions for anæsthetic management are intended as interim recommendations until results correlating electromyographic studies with pulmonary function are completed.[1]

Acknowledgments.—I would like to express my thanks to the many anæsthetists concerned for their co-operation in providing detailed case histories, to Dr. E. A. Blake-Pritchard and Dr. W. Gooddy for allowing me access to their patients, and to Dr. P. Heaf for undertaking the respiratory studies in these patients.

[1]This investigation, now in progress, is being supported by a grant from the Muscular Dystrophy Group, London, and when published will contain detailed references and acknowledgments.

REFERENCES

ANSCOMBE, A. R. (1957) Pulmonary Complications of Abdominal Surgery. London; p. 55.
BASHOUR, F., WINCHELL, P., and REDDINGTON, J. (1955) *New Engl. J. Med.*, **252,** 768.
BENAIM, S., and WORSTER-DROUGHT, C. (1954) *Med. ill.*, **8,** 221.
BOURKE, T. D., and ZUCK, D. (1957) *Brit. J. Anæsth.*, **29,** 35.
BROWN, G. L., and HARVEY, A. M. (1939) *Brain*, **62,** 341.
BUCHTAL, F., and CLEMMENSEN, S. (1941) *Acta psychiat., Kbh.*, **16,** 389.
CAMPBELL, E. J. M. (1958) The Respiratory Muscles and the Mechanics of Breathing. London; p. 47.
CAUGHEY, J. E. (1954) *Thorax*, **9,** 67.
——, and GRAY, W. G. (1953) *V Int. neurol. Congr.*, **2,** 150.
DENNY-BROWN, D., and FOLEY, J. M. (1949) *Trans. Ass. Amer. Phycns*, **62,** 187.
DUNDEE, J. W. (1952) *Anæsth. & Analg.*, **31,** 257.
FELTMAN, J. A., NEWMAN, W., SCHWARTZ, A., STONE, D. J., and LOVELOCK, F. J. (1952) *J. clin. Invest.*, **31,** 762.
FISCH, C., and EVANS, P. V. (1954) *New Engl. J. Med.*, **251,** 527.
GESCHWIND, N., and SIMPSON, J. A. (1955) *Brain*, **78,** 81.
GOODMAN, L. S., and GILMAN, A. (1955) The Pharmacological Basis of Therapeutics. 2nd ed. New York; pp. 128, 133.
GROB, D., LILJESTRAND, A., and JOHNS, R. J. (1957) *Amer. J. Med.*, **23,** 340.
GRUND, G. (1919) *Dtsch. Z. Nervenheilk.*, **64,** 102.
HARVEY, A. M. (1939) *J. Physiol.*, **95,** 45.
HEWER, C. L. (1957) *Brit. J. Anæsth.*, **29,** 180.
JOHNSON, W., and MARSHALL, G. (1915) *Quart. J. Med.*, **8,** 114.
KENNEDY, F., and WOLF, A. (1937) *Arch. Neurol. Psychiat., Chicago*, **37,** 68.
KILBURN, K. H., EAGEN, J. T., and HEYMAN, A. (1959) *Amer. J. Med.*, **26,** 929.
KRAATZ, C. P., and GLUCKMAN, M. I. (1954) *J. Pharmacol.*, **111,** 120.
KRAYER, O., and ACHESON, G. H. (1946) *Physiol. Rev.*, **26,** 383.
LANARI, A. (1946) *Science*, **104,** 221.
LANDAU, W. M. (1952) *Neurology*, **2,** 369.
LODGE, A. B. (1958) *Brit. med. J.*, i, 1043.
MILLER, R. D. (1957) *Ann. intern. Med.*, **46,** 119.
PACHOMOV, N., and CAUGHEY, J. E. (1958) *Aust. Ann. Med.*, **7,** 159.
PATON, W. D. M. (1956) *Brit. J. Anæsth.*, **28,** 475.
PRIME, F. J., and GRAY, T. C. (1952) *Brit. J. Anæsth.*, **24,** 101.
QUILLIAM, J. P. (1955) *Brit. J. Pharmacol.*, **10,** 141.
RICHARDSON, A. T. (1959) Personal communication.
ROWLAND, L. P., HOEFER, P. F. A., ARONSON, H., and MERRITT, H. H. (1956) *Neurology*, **6,** 307.
SECHER, O. (1951) *Acta pharm. tox., Kbh.*, **7,** 231.
SIRNES, T. K. (1954) *Acta pharm. tox., Kbh.*, **10,** Suppl. 1.
SPILLANE, J. D. (1951) *Brit. Heart J.*, **13,** 343.

DISCUSSION

Dr. A. R. Hunter (Manchester) reported the case of a woman aged 54 who had failed to recover normal breathing after an apparently uneventful thiopentone, nitrous oxide, oxygen anæsthetic for hysterectomy. Suxamethonium had been used for intubation and 15 mg of *d*-tubocurarine as a relaxant. Normal respiration had not wholly returned after the

administration of suxamethonium. Neostigmine had been given to the patient when apnœic at the end of the operation and had produced only very inadequate respiration. Repeated doses of nikethamide had produced only temporary improvement in respiration. 10 mg of nalorphine had been apparently more successful but had not completely restored normal breathing. A further 10 mg had evoked no additional improvement.

When first seen seven hours after operation the patient was obviously suffering primarily from carbon dioxide narcosis. This had been brought about by a combination of two factors. First, the left lower lobe was atelectatic and it remained so after bronchoscopy. In addition numerous rhonchi were audible over the rest of the chest. Secondly, the patient had been allowed to continue breathing oxygen from a semi-closed apparatus for some hours while her respiration was insufficient. Washing out of the carbon dioxide by manual hyperventilation and the administration of one litre of M/6 sodium lactate produced a considerable degree of improvement; the limb and face movements returned but the patient still was unable to maintain her colour when breathing air. Further hyperventilation beyond this point, however, merely produced tetany, and when the carbon dioxide combining power of the blood was determined next day it was found to be 18·3 mEq/l. It was therefore apparent that the condition was one of insufficiency of the respiratory muscles rather than failure of carbon dioxide elimination.

Artificial ventilation of the lungs had to be maintained for four days. The return to full pulmonary function was complicated by the development of a pneumothorax which required the insertion of a catheter suction drain. Tracheostomy was performed forty-eight hours after the initial operation. The cuff of the tracheostomy tube was let down for the first time when artificial respiration stopped. The result was a deterioration of the patient's condition, which improved again on inflating the cuff. This sequence of events took place twice again during the subsequent illness. When four weeks after operation the ability to swallow returned the cuffed tracheostomy tube was replaced by an ordinary metal one and this was removed one week later.

The diagnosis in this case proved to be dystrophia myotonica. It should have been made sooner, particularly as the patient had previously had two cataracts operated on, a thyroidectomy and showed marked thinning of the hair. Owing to a misunderstanding, however, it was at first thought that respiratory function had fully returned in the interval between the induction dose of thiopentone, suxamethonium and the administration of *d*-tubocurarine.

This case-history has been given for two reasons. First, the patient required artificial respiration for four days as compared with a few hours required in the cases of dystrophia myotonica reported in the literature. Secondly, dysphagia was outstanding and the patient tended to drown not in her pulmonary secretions but in the saliva and other secretions which she could not swallow but aspirated into her air passages. It would therefore seem that the use of a cuffed tube is of special importance in these cases. This latter point had not been made in the literature.

Finally, Dr. Hunter asked Dr. Kaufman to comment on the fact that the only antidote which improved this patient was nalorphine. This was of interest in view of the fact that other writers on the subject had also commented on the efficacy of this agent.

Dr. J. W. Dundee (Belfast) said that his reported findings with thiopentone and dystrophia myotonica were not so much at variance with Dr. Kaufman's paper as might be imagined. Dr. Kaufman had studied the response to anæsthesia of a large number of patients who were suffering from varying grades of this disease. On the other hand, Dr. Dundee had encountered 2 patients who showed prolonged apnœa following thiopentone and who, on subsequent investigation, turned out to have dystrophia myotonica. This, in fact, was the source of all the published reports on anæsthesia in dystrophia myotonica up to date. In Dr. Dundee's cases an opiate in a fairly substantial dose was given as premedication and he had no doubt that they showed an undue sensitivity to the thiopentone. Dr. Kaufman found a higher incidence of respiratory depression in patients with dystrophia myotonica than would be expected in the population as a whole, and Dr. Dundee was sure that the people who have published reports on this disease had, in fact, encountered very severe cases of it. It was quite possible that all had been wrong in blaming thiopentone and it might, in fact, have been a non-specific response to any anæsthetic agent. Since thiopentone was almost routinely used for the induction of anæsthesia, it was the drug which was given first with which one was most likely to encounter an abnormal response. In Dr. Dundee's patients, the response to thiopentone was so marked that no other agents were needed and naturally it was assumed that this was a specific effect of thiopentone. Dr. Kaufman had, in fact, shown this to be wrong, but nevertheless, there was still a great need for caution when inducing any patient with dystrophia myotonica with thiopentone and it was still recommended that minimal doses be given.

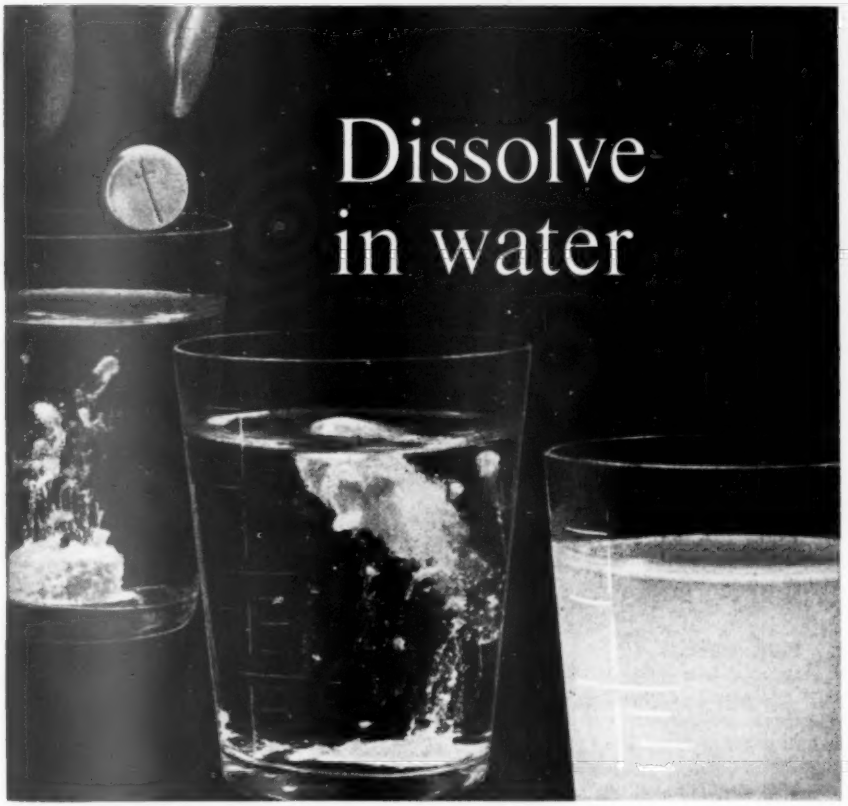
Dr. Kaufman, in reply to Dr. Hunter, said that improvement after nalorphine implied that a morphine derivative had been used at some stage, and this was indeed so, for morphine had been given for premedication.

Dr. Dundee had been the first to draw attention to the marked respiratory response to thiopentone in patients with dystrophia myotonica. However, this response was not specific. Caution should be exercised in administering any central respiratory depressant drug to those suffering from any neurological disorder which was accompanied by diminished respiratory reserve.

(*Meeting to be continued*)

Solprin · Codis · Cafdis

Contain neutral stable soluble aspirin



SOLPRIN. Dissolves in water to form a true solution of calcium acetylsalicylate (neutral soluble aspirin).

Clinical evidence produced over a long period of years indicates that Solprin is unlikely to irritate the gastric mucosa, even in the massive dosage prescribed in rheumatic conditions.

More rapidly absorbed giving a quicker effect.

CODIS. Neutral soluble aspirin with phenacetin and codeine phosphate.

CAFDIS. Neutral soluble aspirin with phenacetin and caffeine.

N.H.S. basic prices for 500 tablets in foil, which ensures protection from moisture:

SOLPRIN 12/6 CODIS 25/- CAFDIS 16/-

Literature and clinical samples available from:

RECKITT & SONS LIMITED, PHARMACEUTICAL DEPARTMENT, HULL, YORKSHIRE

A new preparation!

Puromyn

FOR THE PROPHYLAXIS AND TREATMENT OF INFECTIONS OF THE MOUTH AND THROAT

PUROMYN is a palatable formulation employing the established bactericidal action of neomycin sulphate together with a new fungicide — bis-(2-hydroxy-5-chloro-phenyl) sulphide, which has been shown to exhibit a powerful action in controlling overgrowth of oral fungi.

INDICATIONS. Inflammatory conditions of the mouth and throat and oral moniliasis.

FORMULA. Each tablet contains — neomycin sulphate 5 mg. bis-(2-hydroxy-5-chloro-phenyl) sulphide 40 mg.

PACK. Carton of 20 tablets. Trade Price 2s. 10d. + purchase tax.

CALMIC LIMITED, CREWE, CHESHIRE. Telephone, Crewe 3251 (7 lines)
LONDON: 2 Mansfield Street, W.1. Telephone, Langham 8038/9

Section of Ophthalmology

President—B. W. RYCROFT, O.B.E., F.R.C.S.

Meeting
November 12, 1959

Mr. KENNETH WYBAR read a paper entitled **The Significance of Eccentric Fixation in Squint.**

Meeting
December 10, 1959

THE Meeting took the form of a Forum in which the following panel answered questions from Members of the Section: Mr. C. A. G. COOK, Mr. F. W. LAW, Mr. A. LISTER, Mr. A. B. NUTT, Professor G. I. SCOTT and Mr. E. C. ZORAB.

Meeting
January 14, 1960

Congenital Abnormalities of the Eye with Particular Reference to Prematurity

By C. A. BROWN, F.R.C.S., D.O.M.S.

Bristol

IT is well recognized that there is an increased incidence of general congenital abnormalities in premature infants compared with those born at full term. It is the purpose of this paper to present some of the congenital abnormalities of the eye which have such an increased incidence. "Congenital abnormalities" are taken to mean abnormalities that are detected at or soon after birth and which are due to defects which have developed *in utero* or at the time of birth. A premature infant is defined as one that weighs 5 lb 8 oz or less at birth. The congenital abnormalities to be considered include optic atrophy, squint, cataract, chorioretinitis and myopia.

It is important to realize at the outset that the fact that the child is premature does not mean that the child will be defective, but only that there is an increased likelihood that some defect will be present. Abnormalities in the infant may precipitate premature labour, abnormalities in the mother, like toxæmia, may have had a deleterious effect on the development of the infant *in utero*, and there is also the increased hazard of brain damage during the birth of the premature infant. It is known that the lower the birth weight, the higher is the immediate mortality and the higher the incidence of brain damage, and the more hazardous are the first few weeks of life for the survivors. In a group of 75 children weighing 3 lb or less at birth Drillien (1958) found that three-quarters of those traced (43 children) were of poor mental ability and one-half had a visual defect, amounting to a handicap in one-third. These visual defects were due to retrolental fibroplasia (5 cases), myopia (11 cases, 6 being high myopes), squints (4 cases) and multiple congenital abnormalities (1 case). Similarly Knobloch *et al.* (1956) found that out of 57 infants weighing 3 lb 4 oz or less at birth, 44% had an abnormal condition of some severity, usually neurological and frequently associated with a visual defect, whereas only 8·6% of all premature infants and 2·6% of full-term infants had similar abnormalities.

In a series of 70 babies weighing 3 lb 4 oz or less, Corner (1952) found that 76% were absolutely normal physically and mentally, and the remaining 24% had either some serious neurological lesion (8 cases), retrolental fibroplasia (7 cases), or congenital abnormality (2 cases). The neurological lesions included spasticity, mental retardation and hydrocephalus and caused a high proportion of visual defects.

In cases of *cerebral palsy* the frequency of ocular complications is well recognized, especially optic atrophy—4 in 73 cases (Schrire, 1956); 3 in 100 cases (Breakey, 1955)—and squint—16 in 73 cases (Schrire, 1956); 49 in 100 cases (Breakey, 1955). The optic atrophy may be due to increased intracranial pressure, as in hydrocephalus, cerebral or subdural hæmorrhage, hæmorrhage into the optic nerve or nerve sheath, or to anoxia. Small premature infants are particularly liable to these lesions. With regard to anoxia, Ingram (1956) reported that a group of infants, 60% of whom were premature, had cyanosis and myoclonic twitchings in the first week of life and

subsequently developed optic atrophy. The majority were also mentally retarded.

Congenital squints, which are a frequent complication of birth trauma, may also be due to developmental anomalies or secondary to ocular disease (e.g. congenital cataract). Several workers have reported an increased incidence of squint among children who had been premature at birth (Table I). Thus Hess *et al.* (1934) found that

TABLE I.—SQUINTS IN PREMATURELY-BORN CHILDREN

Author	Total No. of prematures (birthweight less than 5 lb 6 oz)	Percentage of squints among prematures	Percentage of squints in control series
Hess *et al.* (1934) ..	250	14·4%	1·3%
Castrén (1955)	480	4·6%	2·3%

among 250 prematurely-born children 14·4% had squints compared with a 1·3% incidence in a control series of 156 children full-term at birth. Castrén (1955), reviewing a series of 480 premature and 219 full-term children, found an incidence of squints of 4·6% and 2·3% respectively. Brander (1940) found 5·3% of squints among 375 prematurely-born children compared with 0·8% incidence of squints in school children in Finland. Although these figures show a considerable variation (possibly due to the fact that Hess *et al.* included all the premature infants, however handicapped, and Castrén reviewed school children only), they do suggest that this increased incidence of squint is greater than that due to chance. Adopting a different approach Scobee (1951) reviewed a personal series of 230 cases of squint of all ages and found that 31 (13·5%) had been premature at birth, whereas the incidence of prematurity in that part of the United States was 3% (*see* Table II). This too

TABLE II.—PROPORTION OF PREMATURELY-BORN CHILDREN AMONG CHILDREN WITH SQUINTS

Author	No. of prematures	No. of full-term	Percentage of prematures	Incidence of prematurity in author's area
Scobee (1951) ..	31	199	13·5%	3% (U.S.A.)
Fyfe (1960) ..	49	468	9·5%	8% (Scotland)

supports the suggestion that there is an increased incidence of squint among prematurely-born children. On the other hand Fyfe (1960) did not find any significant increase in 442 concomitant squints, 7·9% being premature, but did find an increase in 75 paralytic squints, 18·6% being premature.

In Drillien's series (1958) of 43 children who had been 3 lb or less at birth, 11 (25·5%) had squints. It seems probable that the lower the birth weight, the greater is the incidence of squints.

Congenital cataract —Table III shows a series

TABLE III.—CONGENITAL CATARACT

Type	Premature	Full-term
Rubellar	2	3
Lamellar	7	1
Genetic:		
(*a*) Dominant	—	5
(*b*) Recessive	—	3
(*c*) With aniridia ..	—	3
Post-natal	2	—
Developmental	—	3
In systemic disease ..	—	3
Others	1	8
Total	12	29

of 41 congenital cataracts collected over the last six years, all under 10 years of age As can be seen, there is some evidence that there is an increased incidence of congenital cataract in premature infants in three types: rubellar (40% in premature infants), lamellar (87% in premature infants) and post-natal (100% in premature infants). While the average incidence of prematurity in Bristol in the same period was 7·5%, these figures show that 29% of all cases of congenital cataract occurred in premature infants.

(*a*) *Rubellar cataract* is now a well-recognized disease, being due to maternal rubella in the first three months of pregnancy. According to a prospective enquiry by Hill *et al.* (1958), rubellar defects occur in 50% of all cases of maternal rubella if infection occurs in the first month of pregnancy, in 25% in the second month and in 17% in the third. The infant is small and frequently premature. He is often deaf, mentally retarded and may have congenital heart disease. The cataract is unilateral in 25% of cases; bilateral pigmentary degeneration of the retina, with bilateral macular involvement, is frequent, and occurred in 4 out of 5 cases in this series.

Table IV shows the birthweights of the affected

TABLE IV.—RUBELLAR CATARACTS

	Birth weights	Side	Other defects: Ocular	Other defects: Systemic
Premature A. S.	4 lb 12 oz	R. and L.	Microphthalmos R. and L.	Imbecile
F. C.	3 lb 8 oz	R. and L.	Retinitis R. and L. A.C.S. Nystagmus	Deaf
Full-term W. C.	6 lb 0 oz	L. eye	R. retinitis	—
J. C.	7 lb 0 oz	R. and L.	Retinitis R. and L.	Deaf
J. H.	6 lb 15 oz	R. eye	R. microphthalmos L. retinitis R.C.S. Nystagmus	—

A.C.S.—Alternating convergent squint.
R.C.S.—Right convergent squint.

infants in the author's series. None was over 7 lb and 2 out of 5 were less than 5 lb 8 oz. Similarly Hill *et al.* (1958) found that in 6 of the 8 cases where birthweight was recorded, 4 were premature (4 lb 4 oz, 4 lb 9 oz, 5 lb 6 oz and 5 lb 8 oz) and 2 of low normal birthweight (6 lb 2 oz and 6 lb 7 oz). Associated ocular defects include microphthalmos, nystagmus and squint.

Other ocular complications of rubella include buphthalmos, which is an occasional complication and occurred in 1 case in this series, this being a premature infant.

There was also a case of multiple congenital abnormalities. Here the mother had rubella in the first six weeks of pregnancy and the infant was premature (birth weight 4 lb 15 oz.). There were bilateral colobomata of the iris and choroid, convergent squint, microcephaly, mental retardation, cleft in the upper lip, absent fingers and webbed toes.

(*b*) *Lamellar* (*or zonular*) *cataract* may be present at birth or may develop in the first few weeks after birth. It is the writer's experience that there is an increased incidence of this type of cataract in premature infants.

The majority are thought to be due to a metabolic disturbance in pregnancy (temporary calcium or amino-acid deficiency) or to toxic causes. Hereditary types are excluded from this group. Premature infants have been shown to have amino-acid deficiency in their teeth, and there may be a link here with the cases of congenital cataract with amino-acid crystals in the urine described by Franceschetti (1957). In this series (Table V) there were 7 cases in premature

TABLE V.—LAMELLAR CATARACTS

	Birth weight	General defect: Mother	General defect: Infant
A. *Premature infants*			
J. G.	2 lb 10 oz	—	—
P. S.	3 lb 6 oz	Toxæmia	—
V. W.	2 lb 7 oz	—	—
J. M.	4 lb 8 oz	—	Microcephaly
C. W.	4 lb 10 oz	—	Spastic
C. M.	4 lb 0 oz	—	Mental retardation
P. P.	5 lb 6 oz	Toxæmia	Hypoglycæmia
B. *Full-term*			
M. W.	7 lb 2 oz	—	—

infants and 1 in a full-term baby. 1 infant was spastic, 1 mentally retarded, 1 had microcephaly and 1 had hypoglycæmic attacks. 4 of the 8 also had squints.

(*c*) *Post-natal cataracts.*—2 cases of this type occurred in premature infants (Table VI). The

TABLE VI.—POST-NATAL CATARACTS IN PREMATURE INFANTS

	Birth weight	General condition	Clinical features
M. B.	3 lb 14 oz	Hypothermia	Mature cataracts developed between sixth and tenth weeks
J. H. (one of twins)	3 lb 8 oz	Cord round neck	Mature cataracts developed between sixth and twelfth weeks

eyes were normal up to the sixth week after birth Between the sixth and twelfth weeks, bilateral intumescent cortical cataracts developed, which matured in a few weeks. In one of these cases there was a very low temperature on admission (89° F), and the other had the cord round the neck and had a convulsion after birth. One case of post-natal cataracts in a premature infant has been described by Guy (1954) and one by Ryan (1956), who suggested that an attack of gastro-enteritis in the infant (temperature 104° F) might have been the precipitating factor. Just as cataracts can develop and mature in febrile illnesses like scarlet fever (Duke-Elder, 1940), so toxins or big changes of temperature may be causative factors.

Maternal infections like *toxoplasmosis* cause many congenital abnormalities in the unborn child. The infant is usually premature and frequently suffers from chorioretinitis, hydrocephalus, spasticity, epilepsy and mental retardation. If the mother is affected early in pregnancy the ocular changes are present at birth, but if she is affected late in pregnancy the active phase of chorioretinitis can be seen a few weeks or months after birth. 80% are said to affect the macular area, and the disease is bilateral in 70–85% of cases. A frequent ocular defect is microphthalmos and secondary cataract (often unilateral) and others include iridocyclitis, papillœdema, optic atrophy, nystagmus and squint.

Congenital syphilis is now rare but is usually associated with prematurity. Disseminated chorioretinitis is often present at birth, and in a severe case microphthalmos and secondary cataract may occur.

More recently a new virus disease, cytomegalic inclusion disease, has been described in premature infants. There are severe systemic disturbances, and acute chorioretinitis, optic atrophy and cerebral calcification occur as in toxoplasmosis. Cytomegalic inclusions have been found in the aqueous and the urine in the same case (Burns, 1959). This may well prove to be the cause of cases where the clinical picture is typical of toxoplasmosis but all the tests are repeatedly negative in both mother and child.

High myopia has also been reported to be increased in incidence in premature infants. In his

series of 375 premature children, Brander (1940) reported an incidence of myopia of 2·4% compared with an incidence of myopia of 1·3% in school children in Finland. Eames (1946) in a series of 619 children of whom 155 were premature, reported a slight increase in myopia among those who had been premature. McNeil (1956) reported 4 cases of premature infants who had high myopia which was neither familial nor due to retrolental fibroplasia (of which myopia is a recognized manifestation). Gregory (1957) reported 29 cases of partial retrolental fibroplasia where the incidence of myopia was 85% and one case of high myopia (birth-weight 3 lb) which was neither familial nor related to retrolental fibroplasia. Among 43 children who had been 3 lb or less at birth, Drillien (1958) found 11 cases of myopia (25·6%) 6 being high myopes. (Some of these may have been due to retrolental fibroplasia.)

Temporary myopia of 5 to 20 dioptres is very common in small premature infants in the early weeks of life and usually disappears by three to six months. Cases which persist into childhood may be those few in which the myopia, whatever may be the cause, does not resolve spontaneously. Further work on this subject should help to establish the relationship between myopia and prematurity and also discover the cause of the myopia.

REFERENCES

BRANDER, T. (1940) *Acta paediat., Uppsala*, **28**, Suppl. **1**, 74.

BREAKEY, A. S. (1955) *Arch. Ophthal., Chicago*, **53**, 852.

BURNS, R. P. (1959) *Arch. Ophthal., Chicago*, **61**, 376.

CASTRÉN, J. (1955) *Acta ophthal., Kbh.*, Suppl. **44**, 109.

CORNER, B. D. (1952) *Bristol med.-chir. J.*, **69**, 117.

DRILLIEN, C. M. (1958) *Arch. Dis. Childh.*, **33**, 10.

DUKE-ELDER, S. (1940) Textbook of Ophthalmology. London; **3**, 3162.

EAMES, T. H. (1946) *Amer. J. Ophthal.*, **29**, 57.

FRANCESCHETTI, A. (1957) *Atti Soc. Oftal. ital., Milano*, **17**.

FYFE, A. (1960) In the press.

GREGORY, I. D. R. (1957) *Brit. J. Ophthal.*, **41**, 321.

GUY, L. P. (1954) *Amer. J. Ophthal.*, **38**, 65.

HESS, J. H., MOHR, G. J., and BARTELME, P. F. (1934) The Physical and Mental Growth of Prematurely Born Children. Chicago.

HILL, A. B., DOLL, R., GALLOWAY, T. McL., and HUGHES, J. P. W. (1958) *Brit. J. prev. soc. Med.*, **12**, 1.

INGRAM, H. V. (1956) *Trans. ophthal. Soc. U.K.*, **76**, 133.

KNOBLOCH, H., RIDER, R., HARPER, P., and PASAMANICK, B. (1956) *J. Amer. med. Ass.*, **161**, 581.

MCNEIL, N. L. (1956) *Brit. J. Ophthal.*, **40**, 24.

RYAN, H. (1956) *Amer. J. Ophthal.*, **41**, 310.

SCHRIRE, L. (1956) *S. Afr. med. J.*, **30**, 405.

SCOBEE, R. G. (1951) *Amer. J. Ophthal.*, **34**, 817.

Binocular Vision in Bilateral Aphakia

By N. L. STOKOE, D.O., F.R.C.S.Ed.

Edinburgh

COMPARATIVELY little attention has been paid in the literature to the state of the ocular muscle balance after bilateral cataract extraction, and it has been stated that such patients do not attain stereoscopic vision or that there is a grave danger of diplopia due to heterophoria, particularly if the cataract operations are separated by a long interval of time. The latter view may have arisen from the very early work of Bocci who, in 1895, found that stereoscopic vision recovered readily when (1) the two operations are separated by a short interval, (2) the development of the two cataracts is more or less simultaneous with the minimum interruption of binocular function. He did not succeed in establishing fusion if the interval were long *but postulated nevertheless that fusion first and, later, stereopsis would eventually recover.*

In 1933 Foster and Jackson studied 10 cases of bilateral aphakia of which 50% obtained stereopsis (3 without and 2 with prisms), and concluded that it is worth while removing a second cataract to try to obtain stereoscopic vision if such would assist the patient in his or her mode of living.

Bischler in 1945 studied 50 cases of bilateral aphakia and found that almost all were binocular with single vision on the Worth 4-dot test, had normal amplitude for fusion and good stereopsis. The operation interval varied from several months to eight years.

In 1954 Toselli and Venturi concluded from a study of 17 patients and the available literature that patients who have enjoyed good binocular vision before the development of cataract may, in spite of old age and long operation interval, obtain an excellent restoration of sensorial and motor activity. They added the proviso that aniseikonia, i.e. the relative difference in retinal image size, should not be greater than 5%.

In this short communication on some 61 cases we have followed the latter authors in employing the Worth 4-dot test at 6 metres distance to determine the presence of binocular vision but, unlike them, we have also considered this type of test at reading distance of 33 cm. We have not delved into eikonometry but have made a note where gross anisometropia may lead to size difference.

Heterophoria has been estimated on the

Maddox rod and wing, while the Major amblyoscope, cover-testing and, in some cases, bar-reading have been used to confirm the presence of binocular vision. From a practical point of view it is important to remember the view of Cüppers (1958) that tests employing dissociation to determine the presence of binocular vision do not necessarily represent true binocular balance in free space. Cases which do not fully subscribe to the strict criteria of fusion on the Worth 4-dot test and ability to bar-read for evidence of true binocular vision, may still in some instances show binocularity in practice, as judged by good recovery to the cover test. To simplify matters, however, a tentative classification has been made based on performance on the Worth 4-dot test alone.

Classification (Fig. 1)

The ages of the patients ranged from 40 to 84, the interval between operations from two months to fifteen years, and the tests were performed within a year of the second of these operations.

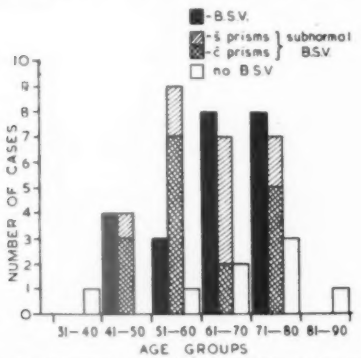


FIG. 1.—Bilateral aphakia. Binocular vision Worth 4-dot test. Age distribution. Three patients treated by muscle surgery have been excluded from this classification. B.S.V.=binocular single vision.

(1) *Binocular single vision* (*B.S.V.*)=fusion on Worth test (4 dots recognized) for distance and near. 23 cases fell into this group, ranging in age from 42 to 78, and are represented by the black columns. In Fig. 1 a greater total population is shown between 61 and 80 merely due to the larger numbers of cataracts coming for treatment in these decades.

(2) *Subnormal.*—(*a*) Requiring prisms to obtain binocular single vision (whether for all distances or near only). These cases numbered 17, represented by the densely cross-hatched columns.

The prism strengths necessary were based partly on the Maddox rod and wing results as a guide, but preferentially on a practical correction of diplopia in the dark room to simulate conditions of "free space". The prism correction was adjusted until a 6/60 letter on the Snellen distance chart, or a line of Jaeger type for near, was seen single.

Quite a number of cases of bilateral aphakia seem in a state of flux for some months after the second operation. Several showing initially either suppression or diplopia on the Worth test have subsequently improved or recovered their binocularity. It is not surprising, therefore, that some of the prisms prescribed were later found to permit reduction. One patient, for example, a man aged 50, gave an initial reading on the Major amblyoscope of -7° R/L 8°–12°, with 10° left excyclophoria, and no fusion, in September 1956 shortly after his second operation. In May 1957, after he had been wearing his full bilateral aphakic correction for some months (without prisms) he was able to fuse with an amplitude of -7° to $+27^{\circ}$, had an objective angle of $+8^{\circ}$ to $+10^{\circ}$ R/L 2°, obtained stereopsis, while in August 1957 he actually succeeded in bar-reading to N5. The cyclophoria disappeared.

(*b*) Variable on Worth 4-dot test. 10 cases were found, indicated by the cross-hatched columns. The majority of this sub-group were binocular for distance and showed an intermittent crossed diplopia for near. As might be expected, there was a large exophoria for near. One or two patients in this sub-section broke down on the Worth test for distance due to esophoria, but apparently fused for near. Vertical imbalance affected one patient preferentially for distance, fusion being obtained for near.

This group of cases obviously requires further attention by the prescription of prisms for, as will be seen later, out of 8 tested 6 showed at least some evidence of stereopsis on the Major amblyoscope (standard slides).

(3) *Non-binocular* (*no B.S.V.*).—These are represented by the non-shaded columns. 8 patients failed entirely on the Worth test (distance and near) with intermittent diplopia or suppression at all distances, and showed no improvement within the period of the investigation. They included manifest divergence (5 cases) or convergence (1 case), a case of alternating hyperphoria, and hypertropia in a patient with old exophthalmic ophthalmoplegia.

Some of this group had less good visual acuity. In the series as a whole, the majority had vision of 6/9 or better, but poor vision in one or other eye obviously militates against a good functional prognosis.

Operations

3 patients underwent muscle surgery and have not been included in the foregoing classification as they form such a small group. Two of these showing divergence were able to fuse with

stereopsis after operative resection of an internal rectus. An illustrative case history is summarized as follows:

Binocular Vision in a Bilateral Aphakic after Internal Rectus Advancement Supplemented by Prisms

Mrs. E. L., aged 58. Operation interval, six years and two months. Second operation 1956.

Dist.: 12 △ Exophoria } Alt. divergence and diplopia
Near: 18 △ Exophoria }

15.1.57: Advancement R. internal rectus

6.2.57: Requires:
Dist.: 2 △ Base up R.
4 △ Base in L.
Near: 2 △ Base up R.
6 △ Base in L.

27.2.57: R
Dist.: 2 △ Base in R. and L.
Near: 4 △ Base in R. and L.

2.9.57: Worth 4 at 6 m.
4 dots at 1 m.
5 crossed diplopia at 33 cm.
Bar-reads N 18.
Suppresses smaller.
Weak stereopsis.

A third patient underwent right external rectus tenotomy but failed to obtain binocular vision, the right eye being readily suppressed. It has been a feature of our cases that suppression occurs readily in the event of any diplopia. Mr. O. M. Duthie of Manchester, who performs bilateral cataract operations at one sitting, stated in 1955 that in his series of 70 cases there was no complaint of diplopia, but his series did not include an analysis of the ocular muscle balance.

Stereopsis (Fig. 2)

The majority of the patients were examined for stereopsis on the Major amblyoscope. Those interpreting both the standard "dots/rings" and "geometrical eight number" slides correctly were said to have full stereopsis, but if only the first and cruder "dots/rings" slide—weak stereopsis.

Full stereopsis was demonstrated on the instrument in 32 out of 47 cases tested (68%), weak stereopsis in 10 (21%). Kruger and Jahner (1958) found stereoscopic vision in 80% of bilateral aphakics examined on the synoptophore, although Guzzinati and Salvi (1957) in their series showed that the stereoscopic acuity was reduced as compared with the normal subject.

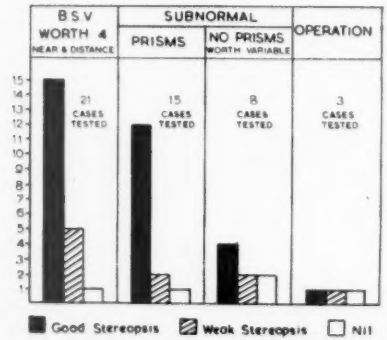


FIG. 2.—Cases showing stereopsis on Major amblyoscope (standard slides).

Inter-operation Interval (Fig. 3)

The extremes were full binocularity after an interval of fourteen years in a woman aged 74, and after two months in a woman aged 44.

Approximately 75% (17 out of 23) of the complete successes occurred with an interval of less than four years between operations, but 25% with an interval over four years. On the other hand, 40% (14 out of 35) of the failures (subnormal or non-binocular) had intervals of over four years.

It is interesting to observe a possible trend in the older age groups of descending percentage success with increasing interval, but considered in small groups the numbers become inadequate for statistical analysis.

One cannot contend the ideal of Mr. Jameson Evans (1958) to operate on both cataracts early, preferably before binocularity has been lost, but it does seem that a long inter-operation interval, even of several years, is not incompatible with recovery of binocular function.

Sex Distribution (Table I)

Here the age and interval groups just referred to have been broadened to give larger constituent numbers. One is surprised to find a persistently higher percentage of success in the females in each group, the total numbers of each sex being approximately equal (30 females to 28 males). The overall majority in favour of the females (57% success to 21%) does not appear to be pure chance, but would require some further investigation.

Discussion (Fig. 4)

It is generally recognized that convergence in the normal has three components: (1) Tonic convergence, (2) accommodative convergence, (3) fusional convergence, and perhaps a fourth, "proximity convergence".

The predominating muscle balance error in this series (in the subnormal B.S.V. group) is an excessive exophoria for near. While this is in some cases related to secondary divergence following the interruption of sensorial activity by cataract, it is interesting to speculate whether in fact the aphakic lacks the "accommodative con-

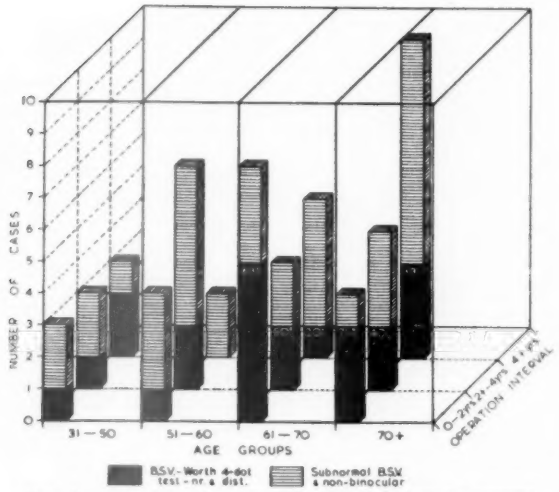


FIG. 3.—Inter-operation interval plotted against age groups.

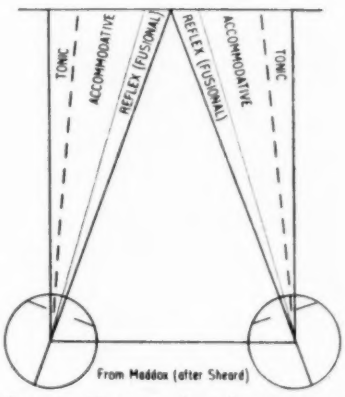


FIG. 4.—Three grades of convergence with fixation at 13 in. (33 cm) (from Tait).

TABLE I.—BINOCULAR VISION IN BILATERAL APHAKIA
Sex Distribution

	Age group 40–60			Age group 61–84			Operation interval 0–2 years			Operation interval Over 2 years			All ages all intervals		
	B.S.V.	Total cases	%	B.S.V.	Total cases	%	B.S.V.	Total cases	%	B.S.V.	Total cases	%	B.S.V.	Total cases	%
Females	4	9	44%	13	21	62%	8	12	67%	9	18	50%	17	30	57%
Males	3	13	23%	3	15	20%	2	7	29%	4	21	19%	6	28	21%

$0{\cdot}01 < p < 0{\cdot}05$

vergence" element and has to rely on fusional convergence or other weaker components.

Tait (1951) states that accommodative and proximity convergence are associative and unnecessary for maintenance of comfortable single binocular vision, but remarks nevertheless that accommodative convergence *can* be demonstrated even in the aphakic. This may be due to continued innervation of the ciliary muscle during near vision in spite of the absence of the lens, and the persistence of a long-established reflex system.

Conclusion

(1) The present work entirely confirms that of previous authors who pronounced a less gloomy prognosis than generally recognized as regards binocular vision in bilateral aphakics.

Recovery from binocular interruption and phoria may not be immediate but may follow after the wearing of the appropriate correctly centred glasses, or by the provision of prisms or by operation.

(2) Prognosis is less dependent on age or interval than on the inherent pre-operative binocular function.

Acknowledgments.—I wish to record my gratitude to the Staff of the Leeds Infirmary Orthoptic Department for their painstaking studies, to Mr. G. Brockbank for all the refraction work, to Mr. J. Foster and Mr. G. W. Black for permission to use their cases, and also to Professor G. I. Scott for his kind interest. My thanks are also due to Mr. S. A. Sklaroff of the Edinburgh University Public Health Department for statistical advice.

REFERENCES

BISCHLER, V. (1945) *Ann. Oculist., Paris*, **178,** 273.
BOCCI (1895) *Ann. Ottalm.*, **24,** (suppl. fasc. 4), 32.
CÜPPERS, C. (1958) Orthoptic and Pleoptic Problems in Germany. Lecture North of England Ophthalmological Society at Leeds.
DUTHIE, O. M. (1955) *Trans. ophthal. Soc. U.K.*, **75,** 25.
FOSTER, J., and JACKSON, A. S. (1933) *Brit. J. Ophthal.*, **17,** 98.
GUZZINATI, G. C., and SALVI, G. (1957) *Ann. Ottalm.*, **83,** 687.
JAMESON EVANS, P. (1958) *Trans. ophthal. Soc. U.K.*, **78,** 577.
KRUGER, K. E., and JAHNER, H. (1958) *Klin. Mbl. Augenheilk.*, **132,** 720.
TAIT, E. F. (1951) *Amer. J. Ophthal.*, **34,** 1093.
TOSELLI, C., and VENTURI, G. (1954) *Ann. Ottalm.*, **80** 241.

The Visual Prognosis in Still's Disease with Eye Involvement

By W. K. Smiley, D.O.M.S., F.R.C.S.

Maidenhead, Berkshire

In the last ten years in the Research Unit for Juvenile Rheumatism at the Canadian Red Cross Memorial Hospital, Taplow, I have examined the eyes of 220 children under the age of 16 with Still's disease. Of this number 12 or 5·5% were found to show evidence of anterior uveitis (5 males, 7 females). They have been followed up for periods varying from two and a half to ten years. This incidence of eye complications is much less than that found in Denmark; Godtfredson (1949) quotes 20% and Vesterdal and Sury (1950) 21%.

The prognosis for vision in my series is not good. Of 12, 8 children had both eyes involved and 4 one eye involved—20 eyes in all. Table I shows their visual acuity at the present time: 50% of the eyes have vision of 6/18 or worse, and

Table I.—Visual Acuity in Still's Disease of 20 Affected Eyes

No. of eyes	Visual acuity	On or off treatment
4	6/9 or better	Off
4	6/9 or better	On
2	6/12	On
2	6/18	On
2	6/36	On
1	6/60	Off
1	Hand movements	Off
1	Perception of light	Off
3	No perception of light	Off

of these half are certifiably blind. Moreover many of the eyes with better vision are still on treatment and it seems likely that the sight of some of these will deteriorate if the causative inflammation persists.

There is no doubt that the longer the anterior uveitis continues, particularly if uncontrolled by local cortisone or small doses of systemic steroids (5–7·5 mg prednisolone daily), the worse the visual prognosis. It should be remembered that the anterior uveitis in this condition persists not for days or weeks but commonly for months or years, even when treated, and tends to recur.

The development of a corneal band opacity is also a bad prognostic sign particularly if it continues to spread despite treatment of the uveitis. 10 out of 12 eyes with vision of 6/12 or less have all had diffuse band opacities. Of 8 eyes with vision of 6/9 or better only one shows a juxta-limbal opacity and this has not spread in several years. Every eye with a diffuse band keratopathy has later developed a complicated cataract. A band opacity which involves the pupil should be removed and this can readily be achieved by chelation of its calcium salts with sodium Versenate after curettage of the corneal epithelium (Grant, 1952; Smiley *et al.*, 1957).

A complicated cataract is much more of a menace to the sight and much less easily removed. Of the 20 eyes in this series 8 have developed mature cataracts and 4 show less advanced lens opacities. In more human terms these 8 mature cataracts occurred in 4 children all of whom have been, or are still, on the Blind Register.

I have operated on 5 eyes of these 4 children and am still in doubt about the best method of tackling the cataract. I needled both eyes of my first patient and also chelated the corneæ. He obtained 6/36 vision in one eye and 6/12 in the other and was able to come off the Blind Register.

Treatment of my second patient was a failure. The needled eye began slowly to degenerate and became shrunken. The only consolation was that his other eye followed the same course some months later without any surgical interference.

The third child came to me after a needling operation elsewhere had also resulted in a blind shrunken eye. The other eye had a cataract and a band opacity. I chelated the corneal band and determined to try and remove the cataract by zonulolysis. A preliminary iridectomy was first performed to see how the eye reacted to operation. Intracapsular extraction was later attempted but defeated by firm adhesions between posterior lens capsule and vitreous face. The capsule ruptured and a curette evacuation had to be carried out. The result was disappointing because the pupil became obliterated by scar tissue which reformed to some extent after each of two subsequent pupillotomies. He now has perception of hand movements but can see to cross a room and negotiate the larger obstacles. He is of course irrevocably on the Blind Register.

My last patient was operated on two months ago, the cornea being chelated and the lens removed intracapsularly at one operation. Again adhesions were encountered between vitreous and lens capsule and in the process of separating these a little vitreous was lost. The eye has settled down well, however, and the final vision should be quite good—enough I hope to remove her name from the Blind Register.

REFERENCES

Godtfredson, E. (1949) *Brit. J. Ophthal.*, **33**, 261.

Grant, W. M. (1952) *Arch. Ophthal., Chicago*, **48**, 681.

Smiley, W. K., May, E., and Bywaters, E. G. L. (1957) *Ann. Rheum. Dis.*, **16**, 371.

Vesterdal, E., and Sury, B. (1950) *Acta ophthal., Kbh.*, **28**, 321.

The following paper was also read:

Sickle Cell Hæmoglobin-C Disease.—Dr. S. S. F. Munro. *See Brit. J. Ophthal.* (1960) **44**, 1.

In all œdematous conditions

HYDRENOX

HYDROFLUMETHIAZIDE

ORAL DIURETIC

offers the following important advantages:-

Hydrenox is at least ten times as potent as chlorothiazide.

The cost of treatment with Hydrenox is lower than with any other potent oral diuretic.

In many cases a single daily dose produces an adequate response.

PACK AND PRICE

Each tablet contains 50 mg. of hydroflumethiazide. Available in containers of 100 and 500 tablets. Basic N.H.S. price 24/- and 116/- respectively. Normal dosage 1-4 tablets daily.

Literature and further information gladly sent on request

BOOTS PURE DRUG COMPANY LIMITED, NOTTINGHAM, ENGLAND

Boots

What does the radiologist require of x-ray film?

1 — MAXIMUM DIAGNOSTIC QUALITY

2 — SPEED

3 — EXPOSURE LATITUDE

4 — KILOVOLTAGE LATITUDE

5 — DEVELOPMENT LATITUDE

All these features are combined in

ILFORD RED SEAL x-ray film

— at the service of radiography

ILFORD LIMITED · ILFORD · ESSEX

Section of Pathology

President—Professor R. J. V. PULVERTAFT O.B.E., M.D.

Meeting
October 20, 1959

THE following papers were read:

Observations on Delayed Radiation Necrosis of the Brain Following X-radiation of the Pituitary Region.—Dr. M. R. CROMPTON.

Circula ory Disturbances in Commo:io Cerebri.—Dr. S. SCHEIDEGGER (Basle).

Familial Poliodysplasia with Leucodys!rophy.—Dr. PETER H. BUXTON.

Meeting
November 3, 1959

SYMPOSIUM ON ENZYME SYSTEMS IN DIAGNOSIS

Dr. K. A. Jegatheesan and **Dr. G. F. Joplin** (London):

The Clinical Value of Serum Glycolytic Enzymes and Acid Phosphatases in Mammary Carcinomatosis [Abstract]

The correlations between certain serum enzymes and the degree of activity of breast carcinomatosis and the site of metastases were assessed to determine the clinical value of the enzyme levels in following the response of the disease to pituitary ablation.

Serial serum enzyme determinations were made in women with advanced mammary carcinomatosis who had a clear-cut clinical response to pituitary ablation by needle implantation of yttrium-90 seeds (Fraser *et al.*, 1959). Pre-implant enzyme levels were measured and serial studies continued for six weeks to eighteen months afterwards. The clinical response of the patients, based on measurement of masses, radiology, calcium metabolism and hæmatology, was graded as "responders" and "non-responders".

Methods.—The total and formol-stable acid phosphatase were determined by the methods of King and Wootton (1956), the tartrate-labile (prostatic) phosphatase by that of King and Jegatheesan (1959); phosphoglucose isomerase and phosphoglucomutase by those of Bodansky (1954, 1957), with slight modifications.

Upper limits of normal for enzyme values.—Total acid phosphatase 3·1 K.-A. units per 100 ml of serum; formol-stable acid phosphatase 2·1, tartrate-labile 0·7 units; phosphoglucose isomerase 25 Bodansky units; phosphoglucomutase 82 Bodansky units.

Results.—Serial serum phosphohexose isomerase estimations gave a close correlation with clinical cancer activity following pituitary ablation. All but one case had raised pre-implant levels. All 7 clinical responders showed a clear isomerase fall during cancer remission, 6 to within normal range. 4 of these were followed to terminal relapse and all showed a concomitant isomerase rise. In the group of 6 clinical non-responders, 3 showed rising isomerase levels, and 2 lowered levels.

Correlation of serum total acid phosphatase with response to pituitary ablation was less striking except when pre-implant levels were greatly raised. However, 5 of the 7 responders did have falls of total acid phosphatase during remission, and the 3 subsequently followed to terminal relapse had rising levels.

Formol-stable and tartrate-labile acid phosphatases were also measured. The formol-stable fraction showed a close correlation with total acid phosphatase, whereas tartrate-labile was invariably normal.

Phosphoglucomutase was followed serially in 10 cases and although there was a slight correlation with post-hypophysectomy alteration in cancer activity, changes were small. Nearly all values lay within the normal range, and day-to-day fluctuation was wide.

Cases were grouped according to the sites of metastases, and their pre-hypophysectomy enzyme levels were compared. 4 of 5 cases with liver deposits had isomerase levels above 80 units, whereas 13 of the 14 cases without liver deposits had levels under 60 units. Mutase showed a less significant although similar trend, but formol-stable acid phosphatase had no correlation with the presence of liver deposits.

Neither isomerase nor mutase levels gave any correlation with the presence or absence of bone metastases. However, a good correlation was found between serum formol-stable acid phosphatase and the presence of bone deposits. 6 of 8 cases with bone deposits had raised formol-stable acid phosphatase, whereas all 8 cases without bone deposits were in the normal range

Enzyme analyses were made on several tissues. The data in Table I show that breast cancer

TABLE I.—TISSUE ENZYME CONCENTRATIONS

		Breast		Bone		Liver	
		Normal	Cancer	Normal	Cancer	Normal	Cancer
Total acid phosphatase (K.-A. units per 100 g)	Range	4·6–77	182–265	103–181	1,594	270–312	306–400
	Mean (No. of cases in brackets)	31 (6)	232 (3)	142 (2)	– (1)	291 (2)	377 (3)
Phosphoglucose isomerase (Bodansky kilounits)	Range	0·004–0·03	0·17	0·3	—	21–40	11–19
	Mean (No. of cases in brackets)	0·02 (2)	– (1)	– (1	—	30 (2)	15 (2)

tissue contains more total acid phosphatase than normal breast tissue. Estimations on a single bone deposit, if confirmed by further work, would readily explain the high serum levels in patients with bone deposits. A high concentration of isomerase in normal liver provides the explanation for the clinical correlation of high serum levels with hepatic deposits (Table I).

Acknowledgment.—We thank Professor E. J. King for help and advice.

REFERENCES

BODANSKY, O. (1954) *Cancer*, **7**, 1191.
—— (1957) *Cancer*, **10**, 859.
FRASER, R., JOPLIN, G. F., LAWS, J. W., MORRISON, R., and STEINER, R. E. (1959) *Lancet*, i, 382.
KING, E. J., and JEGATHEESAN, K. A. (1959) *J. clin. Path.*, **12**, 85.
——, and WOOTTON, I. D. P. (1956) Microanalysis in Medical Biochemistry. London.

Dr. J. H. Wilkinson and **Dr. J. Pryse-Davies** (London):

Enzyme Studies in Myocardial Infarction

The first enzyme test for acute myocardial infarction was introduced by LaDue *et al.* (1954) who reported elevated levels of serum glutamic-oxaloacetic transaminase (S.G.O.T.). This enzyme was first recognized by Braunstein and Kritzman (1937) in preparations of pigeon and rabbit muscle, and it has since been shown to be present in a variety of biological systems. Transaminases catalyse the intermolecular transfer of an amino group from a donor α-amino acid to an acceptor α-keto acid, and in this particular case the amino group from aspartic acid is transferred to α-ketoglutaric acid forming oxaloacetic acid and glutamic acid.

Serum Transaminases in Myocardial Infarction

High concentrations of S.G.O.T. are found in heart muscle and extensive breakdown of this tissue is likely to release enzyme activity into the serum. The spectrophotometric method of Karmen *et al.* (1955) was used for the determination of S.G.O.T. This consists of coupling the transamination reaction to a second system, i.e. the reduction of oxaloacetic acid to malic acid by means of malic dehydrogenase, the hydrogen required being provided by reduced diphosphopyridine nucleotide (DPNH). DPNH differs from the oxidized form (DPN) in having an absorption maximum at 340 mμ. Consequently the fall in optical density per unit time is a measure of the transaminase activity.

Various colorimetric procedures have also been developed but in our experience the spectrophotometric method is more sensitive and reproducible. However, these advantages are marginal, and for most clinical purposes the results given by the colorimetric methods are quite satisfactory.

A related enzyme, glutamic-pyruvic transaminase, is also found in serum (S.G.P.T.) and its activity can be determined by similar methods. S.G.P.T. is markedly raised in liver diseases, especially infective hepatitis.

Typical serial daily results obtained in two confirmed cases of myocardial infarction are listed in Table I. The transient nature of the S.G.O.T. elevation is shown by the return to normal values on the third day in Case I, and on the fourth day in Case II. In the latter the S.G.P.T. was also slightly raised. In both cases the ECG changes supported the diagnosis. Observations in a patient who had two episodes of myocardial infarction are also summarized in Table I (Case III). The S.G.O.T. showed transient rises on each occasion, but the S.G.P.T. remained within normal limits. In this case the ECG was difficult to interpret because of changes due to previous infarction and digitalis therapy, but the diagnosis was confirmed at autopsy. The rise in serum levels soon after the onset of cardiac pain is strongly suggestive of infarction of heart muscle.

TABLE I.—SERIAL DETERMINATIONS OF SERUM GLUTAMIC-OXALOACETIC (S.G.O.T.) AND SERUM GLUTAMIC-PYRUVIC (S.G.P.T.) TRANSAMINASES IN MYOCARDIAL INFARCTION (KARMEN UNITS)

Days after onset of			Case I	Case II		Case III	
1st attack	2nd attack		S.G.O.T.	S.G.O.T.	S.G.P.T.	S.G.O.T.	S.G.P.T.
–2	—		28	—	—	—	—
1	—		82	—	—	65	15
2	—		76	108	48	168	—
3	—		33	84	44	—	—
4	—		33	40	30	108	17
5	—		30	—	—	—	—
6	—		—	—	—	70	15
7	—		—	—	—	50	15
11	1		—	—	—	22	12
12	2		—	—	—	138	12
13	3		—	—	—	74	15
14	4		—	—	—	64	15
15	5		—	—	—	35	19
18	8		—	—	—	33	15

Upper limits of normal: S.G.O.T., 35 units; S.G.P.T., 25 units.

Timing of specimens.—These results demonstrate the transient nature of the elevation of

S.G.O.T. after cardiac episodes and indicate the difficulties of interpretation if only one sample of serum is examined.

Serial twelve-hourly determinations were made in 28 cases. In 6 of these raised values were not found until thirty-six hours after the onset of symptoms, and in 8 a return to normal levels was observed during the second and third days. It is too laborious to perform a daily estimation in each case and we have taken one sample between twelve and twenty-four hours and a second between thirty-six and forty-eight hours after the episode. Frequently the patient is not admitted to hospital until some time after the onset of symptoms and in such cases S.G.O.T. determinations cannot be made until the second, third or fourth day.

Values within the normal range were found in a variety of other cardiac conditions without evidence of infarction, including coronary occlusion, angina pectoris, pericarditis and pulmonary embolism. Agress (1959) has recently reviewed the literature and reported that 96·9% of 1,255 cases of clinically proven myocardial infarction exhibited raised S.G.O.T. values. The small number of cardiac patients who are reported in the literature as having raised S.G.O.T. levels without apparent infarction is attributed by Agress to small undetected infarcts.

The results we have obtained are in substantial agreement with those of other workers, including Chinsky *et al.* (1956) and Baron *et al.* (1958).

In 40 of our cases simultaneous S.G.P.T. determinations were also made. 13 showed values exceeding 25 units/ml on at least one occasion. The highest values, 71 and 69 units/ml, were associated with very high S.G.O.T. figures and might well have been the result of secondary liver damage caused by prolonged hypotension. 2 patients were receiving anticoagulant therapy with a coumarin derivative which was later shown to cause elevation of both transaminase levels. Our experience contrasts with that of Rowell and Smith (1959) who have reported that 23 of their 28 cases exhibited slightly raised S.G.P.T. values.

S.G.O.T. determinations clearly provide an important means of confirming suspected myocardial infarction. This is especially useful when the ECG is equivocal because of previous infarction or other abnormality. False negatives may arise through bad timing in the collection of specimens and false positives as a result of pancreatitis or liver disease. In the latter event simultaneous determination of the S.G.P.T. will aid differentiation.

Though the maximum S.G.O.T. level is probably proportional to the volume of heart muscle destroyed (Nydick *et al.*, 1955), the observed levels in our series appeared to have little prognostic value. Some of the patients with the highest levels recovered, whereas some of those with much lower values died. It may be that several patients died before peak serum transaminase levels were reached.

Other Enzymes

Several other serum enzymes have been investigated in suspected myocardial infarction, particularly lactic dehydrogenase (S.L.D.). Several workers including Kaltenbach *et al.* (1957) found that the elevated S.L.D. persisted longer than S.G.O.T. Though we have confirmed that S.L.D. is raised after myocardial infarction we have not as yet determined the period of elevation. If S.L.D. always remains high for three to seven days after a cardiac infarct, this test may be useful in the assessment of patients from whom blood cannot be collected immediately after the onset of symptoms. Rowell and Smith (1959) report that serum oxidase and aldolase also appear to increase somewhat later than the transaminases.

Acknowledgment.—We are indebted to Dr. S. B. Rosalki for his kind collaboration in this work.

REFERENCES

AGRESS, C. L. (1959) *Amer. J. Cardiol.*, **3**, 74.
BARON, D. N., ALEXANDER, C. P., BELL, J. L., and OAKLEY, C. M. (1958) *Quart. J. Med.*, **27**, 533.
BRAUNSTEIN, A. E., and KRITZMANN, M. G. (1937) *Nature, Lond.*, **140**, 503.
CHINSKY, M., SHMAGRANOFF, G. L., and SHERRY, S. (1956) *J. Lab. clin. Med.*, **47**, 108.
KALTENBACH, J. P., BECKER, J. F., and BERNSTEIN, I. (1957) *Amer. J. clin. Path.*, **27**, 309.
KARMEN, A., WRÓBLEWSKI, F., and LADUE, J. S. (1955) *J. clin. Invest.*, **34**, 126.
LADUE, J. S., WRÓBLEWSKI, F., and KARMEN, A. (1954) *Science*, **120**, 497.
NYDICK, I., WRÓBLEWSKI, F., and LADUE, J. S. (1955) *Circulation*, **12**, 161.
ROWELL, N. R., and SMITH, A. J. (1959) *Brit. med. J.*, ii, 459.

Dr. S. B. Rosalki (London):

Transaminases in Liver Disease

Glutamic-oxaloacetic transaminase (G.O.T.) and glutamic-pyruvic transaminase (G.P.T.) are widely distributed in body tissues, are present in normal serum and are excreted in the bile. Large amounts of G.O.T. are found in liver, cardiac muscle and skeletal muscle, but although G.P.T. is plentiful in the liver, it is low in amount in the other tissues (Wróblewski and LaDue, 1956). After cellular injury the serum levels of these enzymes may be increased, the enzymes presumably leaking from the damaged cells into the blood stream. In liver cell injury considerable increase in the serum levels of both enzymes may take place, but in cellular injury not

involving liver (e.g. myocardial infarction, muscle trauma) increased serum glutamic-oxaloacetic transaminase (S.G.O.T.) activity is not accompanied by a comparable increase of serum glutamic-pyruvic transaminase (S.G.P.T.) activity. Interference with the biliary excretion of S.G.O.T. and S.G.P.T. by obstruction to the outflow of bile is accompanied by increased serum levels of both enzymes.

We have confirmed and extended Wróblewski's original work on the application and assessment of serum transaminase determinations in the investigation of hepatic disease (Pryse-Davies and Wilkinson, 1958; Rosalki *et al.*, 1960). Serial transaminase determinations on over 200 patients with liver disease have revealed characteristic patterns of enzyme changes in the various disease categories (Figs. 1 and 2).

Acute Hepatitis

Infective hepatitis.—In infective hepatitis very high serum levels of both enzymes occur. Early in the disease, at the onset of jaundice, levels were almost invariably over 500 units/ml. (Our normal range using spectrophotometric methods of assay and correction of activities to a temperature of 25° C is 5–35 units/ml for S.G.O.T. and 5–25 units/ml for S.G.P.T.) Enzyme levels fell rapidly within a few days and in uncomplicated cases reached normal levels in two to five weeks from the onset of jaundice. S.G.O.T. activity usually exceeded S.G.P.T. activity in the early phase of illness, but fell more rapidly, so that in many cases S.G.P.T. exceeded S.G.O.T. activity during the recovery phase.

Failure of infective hepatitis to resolve is associated with persistently raised transaminase levels and the development of massive necrosis is accompanied by increasing serum enzyme activity.

Infectious mononucleosis (glandular fever).—Of 45 consecutive cases of infectious mononucleosis (41 sero-positive, 4 sero-negative) 37 showed increased S.G.O.T. activity and 35 increased S.G.P.T. activity. This high incidence is in accordance with the view that hepatitis is an integral feature of most cases of infectious mononucleosis (Leibowitz, 1953). In only 4 of these cases was jaundice present; many showed no clinical evidence of hepatic involvement and minimal or no abnormality of liver function tests. Serum transaminase levels were almost always less than 500 units per ml even in the presence of jaundice, and most were below 200 units per ml. Raised levels were usually present in the early course of the illness, but in contrast to infective hepatitis maximum levels were not reached until the second or third week, returning to normal by the fifth week.

Toxic hepatitis.—Raised transaminase levels ranging up to several hundred units per millilitre have been observed in toxic damage to the liver by salicylate intoxication, chlorpromazine sensitivity and lead poisoning. Raised levels returned rapidly to normal with removal of the toxic agent. No case of carbon tetrachloride poisoning has been encountered but this condition is accompanied by impressive increases of serum transaminase activity (Wróblewski and LaDue, 1955*a*).

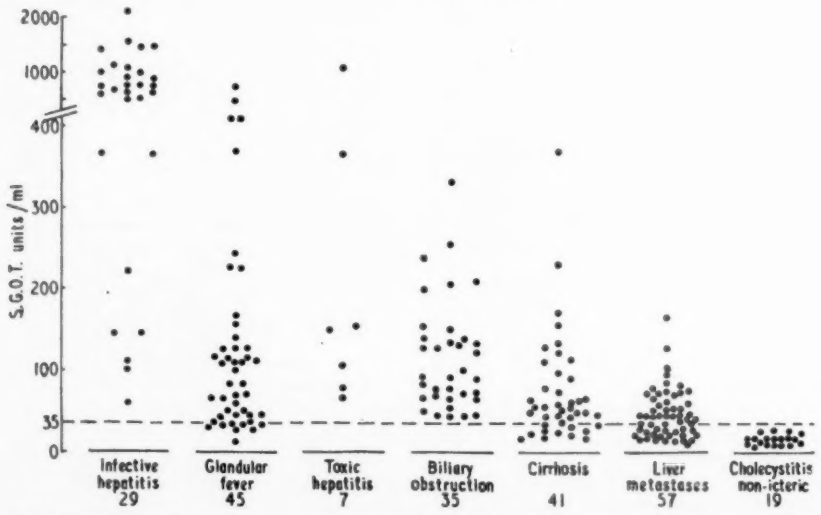


FIG. 1.—Serum glutamic-oxaloacetic transaminase (S.G.O.T.) activities in liver diseases (233 patients).

Obstructive Jaundice

Although S.G.O.T. was always and S.G.P.T. almost always elevated in extrahepatic obstructive jaundice, levels rarely exceeded 300 units per ml. Unlike their course in infective hepatitis, the transaminase levels remained high until the obstruction was relieved and then returned to normal within a week. In most patients with obstructive jaundice the S.G.O.T. level exceeded the S.G.P.T. level. Acute and chronic cholecystitis not associated with biliary obstruction was not accompanied by raised transaminase levels.

Hepatic Cirrhosis

Approximately three-quarters of the cases of cirrhosis showed increased S.G.O.T. activity and one-half increased S.G.P.T. activity. The level of both enzymes, though fluctuating, was usually persistently elevated but rarely exceeded 200 units/ml. No correlation was observed between clinical assessment of liver function and the transaminase levels. Raised serum transaminase levels in hepatic cirrhosis have been associated with histological evidence of liver cell necrosis (Chinsky and Sherry, 1957) and would appear to reflect activity and progression of the disease process, even though they are not a measure of liver function.

Hepatic Metastases

In metastatic carcinoma of the liver the S.G.O.T. level was raised in approximately 50% of cases; S.G.P.T. elevation was less frequent. Levels remained below 200 units/ml and, as in cirrhosis, persistent though fluctuating levels were observed. Deterioration or improvement in the malignant condition in response to therapeutic measures was reflected by elevation or depression, respectively, of serum enzyme levels. It was unusual for transaminase elevation not to be accompanied by raised values of serum alkaline phosphatase. A raised transaminase accompanying an elevated alkaline phosphatase level indicates hepatic involvement. Malignant deposits in bone, or bone disease, give rise to serum alkaline phosphatase elevation unaccompanied by raised transaminase levels (Wróblewski and LaDue, 1955*b*).

Conclusions

In general our observations are in agreement with other workers. However, S.G.O.T. was more frequently abnormal than S.G.P.T. in each variety of liver disease. Even in early infective hepatitis and obstructive jaundice S.G.O.T. levels generally exceeded S.G.P.T. levels, an observation at variance with those of Wróblewski and LaDue (1956) and Henry (1959) but in agreement with those of Latner and Smith (1958) and, with respect to obstructive jaundice, with De Ritis *et al.* (1956).

Transaminase determination has proved of considerable diagnostic assistance in the detection of acute and chronic hepatocellular disease, the differentiation of the jaundice of infective hepatitis from that of extrahepatic biliary obstruction and in the detection of hepatic metastases.

It is important to stress that transaminase

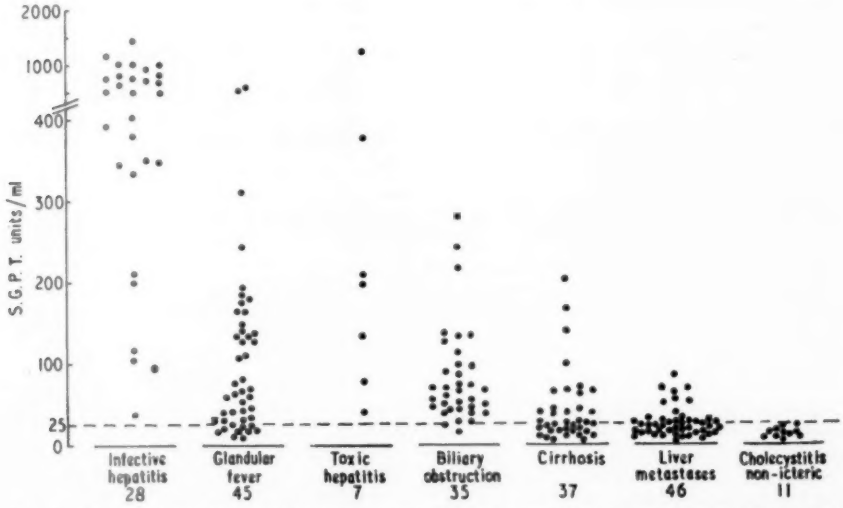


FIG. 2.—Serum glutamic-pyruvic transaminase (S.G.P.T.) activities in liver diseases (209 patients).

elevation (in the absence of biliary retention) provides an indication of liver cell injury and does not express liver cell function. Transaminase determination appears to be a most sensitive indicator of liver cell damage and raised levels may reveal liver disease at a time when conventional liver function tests are normal. The greatest degree of diagnostic precision is obtained when transaminase determinations are made early in the course of illness, serial observations at suitably timed intervals are performed, and the tests are interpreted in the light of clinical information and in conjunction with conventional tests of liver function.

REFERENCES

CHINSKY, M., and SHERRY, S. (1957) *Arch. intern. Med.*, **99**, 556.

DE RITIS, F., COLTORTI, M., and GIUSTI, G. (1956) *Minerva Med.*, **1**, 167.

HENRY, L. (1959) *J. clin. Path.*, **12**, 131.

LATNER, A. L., and SMITH, A. J. (1958) *Lancet*, ii, 915.

LEIBOWITZ, S. (1953) Infectious Mononucleosis. New York.

PRYSE-DAVIES, J., and WILKINSON, J. H. (1958) *Lancet*, i, 1249.

ROSALKI, S. B., *et al.* (1960) *Brit. med. J.* In the press.

WRÓBLEWSKI, F., and LADUE, J. S. (1955*a*) *Ann. intern. Med.*, **43**, 345.

——, —— (1955*b*) *Cancer*, **8**, 1155.

——, —— (1956) *Proc. Soc. exp. Biol., N.Y.*, **91**, 569.

Meeting
November 17, 1959

LABORATORY MEETING AT THE CENTRAL PUBLIC HEALTH LABORATORY, COLINDALE AVENUE, LONDON

THE following demonstrations were given:

Central Enteric Reference Laboratory

Bacteriophage Typing of Salmonellas.—A. BERNSTEIN.

Fluorescence Microscopy in the Study of Normal and Virus-infected Bacteria and Tissue Cultures.—E. S. ANDERSON.

Standards Laboratory

Diphtheria Antitoxin Titrations in Guinea-pigs.—P. BRADSTREET and M. BAILEY.

(1) Spectra of Antibody Responses to Immunization in Rabbits with Various Salmonella Organisms. (2) Preparation of Specific Diagnostic Antisera by Absorption.—J. EDWARDS.

Preparation and Standardization of Bacterial Agglutinable Suspensions for Serological Diagnosis.—W. BRADLEY.

Preparation and Standardization of Virological Diagnostic Reagents.—M. HULLY.

Routine Diagnostic Laboratory

Routine Procedure for the Isolation of Viruses in Cell Culture.—C. E. D. TAYLOR.

Salmonella Reference Laboratory

(1) Routine Identification of Salmonellæ. (2) Biochemical and Other Tests Used in an Attempt to Differentiate Human from Animal Types of *S. paratyphi B.*—MARGARET LEE and JOAN TAYLOR.

Fluorescent Antibody Staining of Cultures and Human Faces.—M. PATRICIA WILKINS.

Histology of Rabbit Gut Used as a Test for Enteropathogenicity.—JACK PAYNE.

Ligated Rabbit Gut as a Test for the Enteropathogenicity of Organisms.—JOAN TAYLOR and M. PATRICIA WILKINS.

Dysentery Reference Laboratory

(1) Identification of Shigellæ. (2) Major Biochemical Tests for Group Differentiation within the Enterobacteriaceæ.—K. CARPENTER and M. DAVIES.

Colicine Typing of *Shigella sonnei*.—M. DAVIES.

Streptococcus, Staphylococcus and Air Hygiene Laboratories

The Use of Fluorescent Antibody for the Rapid Diagnosis of Infections with Hæmolytic Streptococci.—H. GOODER.

Electrophoretic Study of Ionizable Groups at Bacterial Surfaces.—D. PLUMMER and A. M. JAMES.

Protoplasts and L Forms of Hæmolytic Streptococci.—H. GOODER and W. R. MAXTED.

Investigations of Epidemics of Staphylococcal Infection in Hospital.—M. PATRICIA JEVONS.

A Rapid Screening Method for Recognizing Carriers of Type 80 Staphylococci.—ELIZABETH H. ASHESHOV.

Investigations of the Ventilation of Hospital Operating Theatres.—O. M. LIDWELL and R. E. O. WILLIAMS.

The Distribution of *Cl. welchii* in Air Samples from Hospital Wards.—W. C. NOBLE.

Virus Reference Laboratory

Enteroviruses.—A. D. MACRAE.

Coxsackie Viruses.—D. R. GAMBLE.

The Quantitative Measurement of Tissue Culture Growth.—M. E. ROWATT.

New Respiratory Viruses.—M. S. PEREIRA.

Pox Viruses of Man—Some Practical Uses of Gel Diffusion in the Virus Laboratory.—M. H. HAMBLING and F. O. MACCALLUM.

National Collection of Type Cultures

Fallacies of the Nitrate Reduction Test.—K. J. STEEL.

Contaminants of HeLa Cell Cultures.—J. MIDGLEY.

Lecithinase Reaction in Plate Culture of Clostridia.—H. E. ROSS.

Freeze-drying Techniques.—P. J. FISHER.

whatever the situation

. . . relief is always within reach

Immediate action is the key to successful treatment of migraine. And 'Migril' is tailor-made for such action. The tablets can be taken anywhere—at any time—to avert an attack. And thanks to their adequate content of ergotamine, they provide really prompt relief. Each tablet contains 2 mgm. ergotamine tartrate; yet this dosage can be taken with minimal risk of nausea or vomiting—for 'Migril' also incorporates the powerful anti-emetic, cyclizine hydrochloride. Caffeine is added, too, to potentiate the action of ergotamine. For these good reasons the patient who carries 'Migril' carries constant insurance against attacks.

'migril' TRADE MARK . . . *means more intensive*

action against migraine

Each compression-coated tablet contains ergotamine tartrate, 2 mgm; caffeine (alkaloid), 100 mgm; cyclizine hydrochloride, 50 mgm. In bottles of 10 and 100.

BURROUGHS WELLCOME & CO.

(THE WELLCOME FOUNDATION LTD.)

LONDON

That gnawing ache . . .

The pain brought on by peptic

ulcer is quickly relieved by Pro-Banthine—

pre-eminent in this field.

Pro-Banthine

In cases where peptic ulcer is
complicated by emotional overlay
PRO-BANTHINE WITH DARTALAN
is available as a compound tablet
containing Pro-Banthine 15 mg.
and Dartalan 3 mg.

SEARLE HIGH WYCOMBE, BUCKS

Section of Physical Medicine

President—BASIL KIERNANDER, M.R.C.P.

Meeting
November 11, 1959

The Blood Supply of the Brachial Plexus

By SAJIDA ABDULLAH, M.Sc., M.B.,[1] and RUTH E. M. BOWDEN, D.Sc., M.B.
London

CLINICAL observation suggests that vascular insufficiency might contribute to the onset of brachial neuritis associated with disease of the cervical spine. Omissions and discrepancies in the literature of the detailed general and vascular anatomy of the plexus (Abdullah, 1958) prompted yet another study of the subject. The findings summarized here are based on studies of 118 plexuses of dissecting-room cadavers and 8 fœtal and 30 adult plexuses injected with Neoprene latex (the adults ranged from 49 to 87 years of age). Movements of dural sheaths, spinal cord and nerve roots in relation to bone were observed in four unfixed fœtuses (26, 27, 32 and 34 weeks respectively), a male of 14 and a female of 19 years.

The blood supply of the brachial plexus is dependent upon the subclavian artery and its derivatives, but there is some disagreement about the precise branches involved (Adamkiewitz, 1886; Bartholdy, 1897; Tonkoff, 1898; Bergmann and Alexander, 1941). Amongst the vessels cited are the vertebral, the ascending and deep cervical and the superior intercostal arteries, and all these vessels were observed to play some part (Fig. 1). The origin of the vertebral artery may vary and frequently the left is somewhat larger than the right vessel (Thane, 1899; Adachi, 1928) (Fig. 2); both may undergo gross distortion as a result of osteoarthritic changes in the spine (Biemond, 1951; Hutchinson and Yates, 1956). The main vessels supplying the plexus were symmetrically arranged

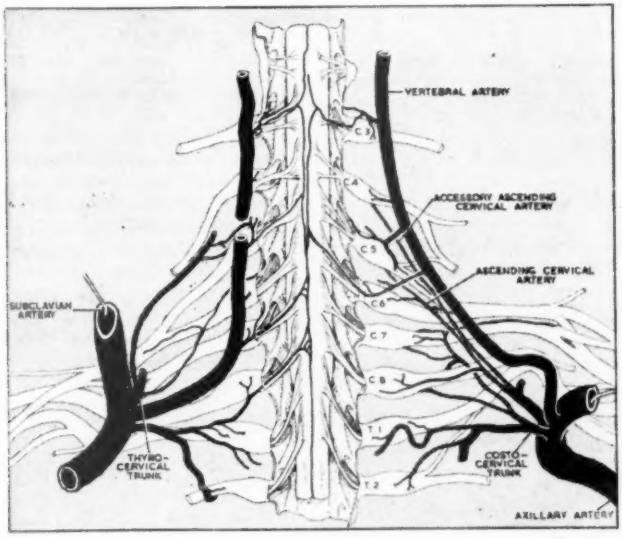


FIG. 1 (*Case* 2).—Anterior view of the blood supply of the right and left brachial plexuses. The proximal ends of both subclavian arteries have been retracted and displaced upwards and laterally to display the origin of branches more clearly. (Drawn by A. Besterman.)

[1]Present address: The Fatimah Jinnah Medical College for Women, Lahore, West Pakistan. The work reported here was supported by a Grant from the Medical Research Council and formed part of a thesis entitled "Studies on the Anatomy of the Human Brachial Plexus with special reference to its Blood Supply" for which the degree M.Sc. was awarded by the University of London.

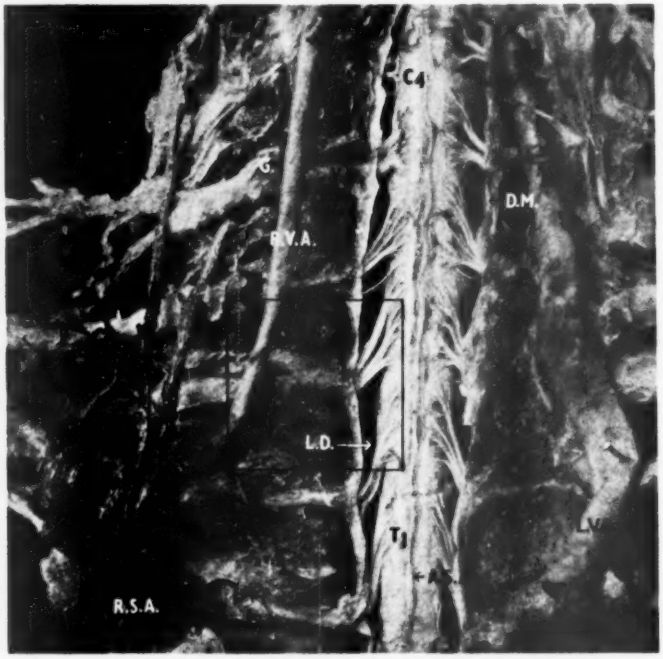


FIG. 2 (*Case* 11).—(Anterior view.) Note the inequality in size of the right (R.V.A.) and left (L.V.A.) vertebral arteries. The latter shows early signs of distortion.

C_4 and T_1 = Anterior rootlets of fourth cervical and first thoracic nerves respectively.
A.S.A. = Anterior spinal artery.
D.M. = Cut edge of dura mater.
G. = Ganglion of fifth cervical nerve.
L.D. = Ligamentum denticulatum.
R.S.A. = Right subclavian artery.

Note branches from the vertebral arteries which pass medially (M.Br.V.A.). In square, note the right seventh cervical nerve in relation to the pedicles of the sixth and seventh cervical vertebræ.

in 6 out of 17 bodies, but there was variation in the minor vessels. The cord and rootlets of cervical nerves were supplied by the anterior and posterior spinal branches of the vertebral artery, and these were reinforced through the intervertebral foramina by segmental vessels from the cervical part of the vertebral, the ascending and deep cervical and the superior intercostal arteries. In a detailed study of the arterial supply of the ganglia, that of the seventh was found to be most variable (Tonkoff, 1898; Bergmann and Alexander, 1941). The ganglionic vessels either passed straight backwards or were derived from medial and lateral branches of the vertebral artery, and other branches arose from the superior cervical and intercostal vessels. The medial branches of the vertebral artery also supplied bone and joints of the vertebral column, and disease or distortion of the vessel might well accelerate degenerative changes in these structures. The trunks of the plexus were supplied directly or indirectly by muscular branches of the ascending and deep cervical arteries and superior intercostals, and occasionally from the subclavian itself. The cords received small direct branches from the subclavian, axillary and subscapular vessels. In this series there were no vasa nervorum from the suprascapular and transverse cervical arteries (Tonkoff, 1898; Ramage, 1927).

The veins could not be studied in great detail. Venules running along with nerve roots traversed the dural ostia to open into the internal vertebral venous plexus behind the roots; occasionally the vessels pierced the dura above or below the ostia and opened into the same venous plexus, which also received vessels from the medial parts of the relevant ganglia. The lateral part of the ganglia drained either through muscular veins or directly into the plexus around the vertebral artery, or into tributaries of the superior intercostal vein. In the more distant parts of the plexus the veins drained into the tributaries of the axillary and subclavian veins.

Histological preparations made by the Pick-

worth sodium nitroprusside benzidine technique (1934) demonstrated three distinct patterns in the intrinsic vascular arrangements. The anterior and posterior roots of nerves were supplied by a coarse plexus of vessels running parallel with the nerve bundles, and connected together at irregular intervals by fine transverse vessels. The dense capillary bed in the ganglia was more conspicuous at the poles and periphery. In some of the ganglia irregular dilatations were seen (Bergmann and Alexander, 1941; Blunt, 1956), and in central sections vessels were seen to run an arcuate course between the anterior and posterior nerve roots. The third type of pattern, typical of peripheral nerves, was found in the spinal nerves which had an epineural plexus of larger vessels and a well-defined plexus of longitudinal vessels converted into a fine meshwork by transversely arranged linking capillaries.

Several details of general anatomy not commonly recognized emerged from this study, and together with the vascular patterns they may be of clinical significance. The number of bundles forming anterior nerve roots varied from 1 to 6 (it is usually stated to be 2), and in only 7 out of 74 nerves was a single bundle seen to pass through the dural ostium; in the remaining 67 the separate bundles and their accompanying vessels passed through the single opening in the dura. In 76 posterior roots, the bundles entering the ostium ranged from 2 to 10 in number. Whilst the direction of bundles forming nerve roots was in general downwards, that of individual bundles forming a single root varied and the lower ones might pass downwards, horizontally or even upwards to the ostium. The roots of the highest nerves of the plexus were related to a single intervertebral disc, but the upper bundles of the eighth cervical and first thoracic nerves were invariably related to two discs, and the lowest to a single one.

It is of interest to note that while the movements of the dural sleeves confirmed those reported by Frykholm (1951) the movements of nerve roots did not conform to those of the dura, and rotation of the head and neck showed differences in the relative positions of anterior and posterior nerve roots. The well-known exaggeration of angulation occurs where the discs and joints of Lushka have degenerated and the total length of the vertebral canal is reduced.

The normal anatomical arrangements indicate that there are constant shearing stresses between nerve roots and the relatively fixed and adherent dura with risk of repeated minor vascular injury (Frykholm, 1951; Brain *et al.*, 1952). Where disease or damage of unyielding bony structures distorts or narrows the main dural sac or sleeves this risk is increased, and it seems likely that the intrinsic arcuate vessels might be particularly vulnerable. This same disease may also distort the vertebral artery. The seventh cervical nerve has a more variable blood supply; sometimes the bulkiest nerve root, it lies at the level of maximum excursion of the cervical spine. The nerve roots and the nerves themselves change direction at the dural ostium, and the tips of transverse processes. Before reaching the latter, the spinal nerve sheaths may give origin to fibres of scalenus anterior and medius, muscles which are active during respiration (Weddell *et al.*, 1944; Kirgis and Read, 1947; Frykholm, 1951). On this and other evidence it is suggested that greater weight should be given to vascular damage as an ætiological factor in brachial neuritis.

Acknowledgments.—It is a pleasure to record our thanks to the Medical Research Council for a generous grant towards expenses; to the Pathologists of the Royal Free Hospital; to Professor Dorothy Russell of the Bernhard Baron Institute of Pathology of the London Hospital; and to the technical staff of the Anatomy Department of the Royal Free Hospital School of Medicine. One of us (S. A.) is indebted to the Fatimah Jinnah Medical College for Women for study leave, and to the Government of Pakistan for a personal grant.

REFERENCES

ABDULLAH, S. (1958) *see* M.Sc. Thesis, London, for a review of the literature.

ADACHI, B. (1928) Das Arteriensystem der Japaner. Kyoto; **1**, 148.

ADAMKIEWITZ, A. (1886) Der Blutkreislauf der Ganglionselle. Berlin.

BARTHOLDY, K. (1897) *Morph. Arb., Jena*, **7**, 393.

BERGMANN, L., and ALEXANDER, L. (1941) *Arch. Neurol. Psychiat., Chicago*, **46**, 761.

BIEMOND, A. (1951) *Brain*, **74**, 300.

BLUNT, M. J. (1956) Ph.D. Thesis, London.

BRAIN, W. R., NORTHFIELD, D., and WILKINSON, M. (1952) *Brain*, **75**, 187.

FRYKHOLM, R. (1951) *Acta chir. scand.*, **101**, 345; **102**, 10, 93; Suppl. 160.

HUTCHINSON, E. C., and YATES, P. O. (1956) *Brain*, 79, 319.

KIRGIS, H. D., and READ, A. F. (1947) *Anat. Rec.*, **97**, 348.

PICKWORTH F. A. (1934) *J. Anat., Lond.*, **69**, 62.

RAMAGE, D. (1927) *J. Anat., Lond.*, **61**, 198.

THANE, G. D. (1899) In: Quain's Elements of Anatomy. 10th ed. London; **2**, Pt. II, p. 419.

TONKOFF, W. (1898) *Int. Mschr. Anat. Physiol.*, **15**, 353.

WEDDELL, G., FEINSTEIN, B., and PATTLE, R. E. (1944) *Brain*, **67**, 178.

Steroid Osteoporosis [*Abridged*]

By P. Hume Kendall, M.R.C.P., D.Phys.Med.

London

At the present time there are two main theories to account for the generalized skeletal decalcification that follows prolonged steroid therapy. The first of these is that the weakened bone structure results from a defect in the formation of bone matrix; it is suggested by Reifenstein (1956) that this is due to an anti-anabolic action of adrenocortical steroids on protein and osseous tissue rather than catabolic activity. Although he does not produce any direct evidence to support this thesis, he cites the increased nitrogen excretion that invariably follows corticosteroid administration. West (1958) contests this view that there is a depletion of the body protein stores, and from the results of a considerable number of creatinine balance studies shows that the increased protein excretion is more than sufficiently compensated by an adequate dietary protein intake.

As an alternative theory, West (1957) states that the decreased bone density results from excessive calcium output. That the latter occurs has been clearly demonstrated by Sprague *et al.* (1950) and Morgan *et al.* (1956) who show that increased intestinal excretion is the main source of the loss. Van Buchem (1959) also suggests that increased calcium excretion may be the cause of the osteoporosis and indeed reports one patient in whom the results of calcium loading tests indicated that osteomalacia had developed. He concludes that this disease may well account for some of the cases of "osteoporosis" associated with adrenocortical administration. Further investigation seemed necessary to confirm or reject this novel idea.

The present study.—5 patients were selected who showed the most advanced changes among more than 70 on prolonged steroid therapy. The degree of involvement of the vertebral bodies and the fact that each had suffered one or more fractures was also considered. A full radiological survey, repeated serological and calcium loading tests were performed, and biopsy specimens of the vertebral bodies and iliac crest were examined histologically. None of the affected patients was on a dose level of less than 15 mg prednisone daily or its equivalent cortisone analogues. As only 32 of the overall group were on this dose the incidence of severe porosis was 16% in the present series.

Radiological survey.—The vertebral bodies, pelvis, long bones, ribs and feet were the main sites of osteoporosis in order of frequency (*see* Table I). This order of appearance of bone involvement is similar to the classical distribution of osteoporosis described by Cooke (1955). The reduction in bone density was generalized and associated with increased trabecular markings, expansion of the intervertebral discs into the bodies and collapse and wedging of the vertebræ. None of the specific areas of transformation described by Looser (1920) was observed. With the exception of the latter, however, the features were those that might follow either advanced osteoporosis or osteomalacia.

Table I.—Clinical Details of Patients Investigated

Case	Sex	Age	Drug	Duration	Site of porosis
I	F	64	Triamcinolone	18 months	Spine—pelvis—femur
II	M	38	Triamcinolone	2 years	Spine—pelvis—ribs
III	M	55	Prednisone	4 years	Spine—pelvis—long bones—foot
IV	F	54	Prednisone	4 years	Spine—all long bones—humerus
V	M	47	Triamcinolone	20 months	Spine—pelvis

Calcium loading tests.—The serum calcium, phosphorus and phosphatase levels were normal on repeated examination. The calcium × phosphorus product lay between 35 and 44 which was, again, normal. All other serological investigations were normal for patients suffering from rheumatoid arthritis; there was no Bence-Jones proteinuria.

At the time that the investigation was undertaken, facilities for strontium balance studies were not complete, so use was made of the calcium loading tests described by Finlay *et al.* (1956) as providing the most useful way of demonstrating osteomalacia. These tests are based on the fact that after intravenous infusion of calcium in osteomalacia, the calcium disappears rapidly from the blood and only small quantities appear in the urine. In osteoporosis the calcium is absorbed more slowly from the blood and is excreted into the urine in normal quantities. Normal excretion is 33–53% within twelve hours whereas in osteomalacia less than 26·8% is excreted.

In the 5 patients so far examined by this method the retention and excretion levels were well within normal limits (*see* Table II).

Histology.—The histological diagnosis of osteomalacia depends upon the recognition of broadened osteoid seams which stand out clearly from the normally calcified matrix of the trabeculæ.

TABLE II

Case	Serum calcium	Serum phosphorus	Alkaline phosphatase	Urinary excretion of calcium (Percentage*)
I	10·9	3·2	16	38·0
II	9·8	3·9	4	41·9
III	11·1	4·0	14	33·0
IV	10·6	3·9	9	52·1
V	10·4	3·3	12	47·3

*Normal range of calcium excretion = 33–53%.

Various methods of decalcification exist to demonstrate the osteoid borders; that described by Meyer (1956) is probably the most satisfactory for normal use and was followed by a variety of staining methods.

In each patient at least two biopsy specimens of bone were obtained, one from the most severely involved vertebral body and the other from the iliac crest. Macroscopically the specimens of bone were exceedingly soft and fragile. The biopsy needle (which is a toothed instrument measuring 3 mm in diameter) penetrated the cortex with a minimum of effort, indeed more resistance was met from entry into the intervertebral discs.

Microscopically there was gross thinning of the cortex, the trabeculæ were fewer in number and thinner than in normal bone. A most marked and significant feature was the very considerable reduction in the number of osteoblasts present; osteoclasts were almost entirely absent. In no specimen were the osteoid borders increased, nor were there any of the other features usually associated with decalcification. The picture was, in fact, that of advanced bone atrophy, the result of defective bone formation, classical of osteoporosis.

Conclusions.—It is clear that none of the patients in the present series was suffering from osteomalacia. In view of the increased calcium output, it would seem wise, nevertheless, to consider this possibility in any patient who develops a generalized decalcification whilst on steroid therapy; even though calcium excretion is increased in these patients the total loss is not great and it would probably require a superimposed dietary deficiency for osteomalacia to develop. As the majority of patients on steroids are under close supervision, this would seem to be an unlikely combination of events.

Microscopically, the changes appeared to be similar to those of idiopathic or senile osteoporosis, and so also were the radiological and serological changes. Clinically, however, it is interesting that although the patients showed the classical features of the disease, they did not fall into the accepted age groups and sex incidence. Thus although the final histological picture of steroid osteoporosis is identical with the more commonly recognized forms, i.e. a defective formation of the matrix, associated with a gross reduction in the number of osteoblasts, it seems unlikely that the physiological changes that result in this pattern are similar.

The reason for this defection of the osteoblasts is by no means certain. It may well be that in the older age groups the osteoporosis is one feature of widespread degenerative changes and in this respect it is interesting to note that most patients with osteoporosis show other stigmata of a degenerative nature, viz. atrophy of the skin, loss of hair, arcus senilis, &c. It would be unreasonable to suggest that this could also be the result of steroid therapy. Reifenstein (1958) considers that all patients undergoing adrenocortical administration should concomitantly receive small doses of anabolic steroids to reduce protein depletion. Although West's work suggests that this is an unnecessary measure, it would appear that prolonged administration of anabolic steroids in osteoporosis does result in the relief of pain and occasionally in recalcification of bone (Albright, 1947), and indeed several of the patients reported here have experienced relief of symptoms from anabolic steroids. For these reasons it seems possible that the action of anabolic steroids is the result of an endocrine activity rather than any passive effect in reducing nitrogen or calcium excretion. The relationship between osteoporosis and the hormones secreted by the male and female sex glands is complicated by the presence of hormones with similar actions secreted by the adrenal cortex. Albright (1947) has suggested that not only do women undergo a menopause, but that both sexes undergo an "adrenopause". Thus it may be that there is a hormonal factor common to all forms of osteoporosis; in the senile and idiopathic forms, the deficiency resulting from selective atrophy of the adrenal cortex and in the steroid osteoporosis from suppression of it.

REFERENCES

ALBRIGHT, F. (1947) *Ann. intern. Med.*, **27**, 861.

BUCHEM, F. S. P. VAN (1959) *Lancet*, i, 933.

COOKE, A. M. (1955) *Lancet*, i, 877, 929.

FINLAY, J. M., NORDIN, B. E. C., and FRASER, R. (1956) *Lancet*, i, 826.

LOOSER, E. (1920) *Dtsch. Z. Chir.*, **152**, 210.

MEYER, P. C. (1956) *J. Path. Bact.*, **71**, 325.

MORGAN, H. G., MITCHELL, R. G., STOWERS, J. M., and THOMSON, J. (1956) *Lancet*, i, 925.

REIFENSTEIN, E. C., Jr. (1956) *Sth. med. J.*, **49**, 933.

—— (1958) *Metabolism*, **7**, 1.

SPRAGUE, R. G., *et al.* (1950) *Arch. intern. Med.*, **85**, 199.

WEST, H. F. (1957) *Ann. Rheum. Dis.*, **16**, 322.

—— (1958) *Lancet*, ii, 877.

Early Radiographic Signs of Rheumatic Disease

By A. C. Young, M.B., D.M.R.D.

London

Film densities and contrasts vary between normal individuals and density differences alone are not reliable criteria of pathological change, but the structural details of bone are recognizable over a wide range of X-ray qualities and give direct evidence of destruction and new bone formation.

Radiological anatomy (Fig. 1).—The normal metacarpal has two dorsal ridges near its head which show as roughly longitudinal condensations in the X-ray film. The cortex of the shaft is thick and thins out in a trumpet-like expansion at the neck. The trabeculæ immediately beneath the articular cortex are palisaded at right angles to it. More deeply they form a honeycomb. They arise from the sides of the shaft longitudinally and tend to sweep towards the radial side of the head. The line of synovial attachment is on the contour of the bone radially, but tends to be obscured by the ulnar ridge on the other side. (This explains the easier recognition of lesions on the radial side, also the late involvement of the dome of the articular cortex since destructive lesions occur first at the synovial attachment.)

As a basis for detecting abnormality (1) the cortex should have appropriate thickness and shape; and (2) the trabeculæ should join the cortex, be well seen and of regular pattern.

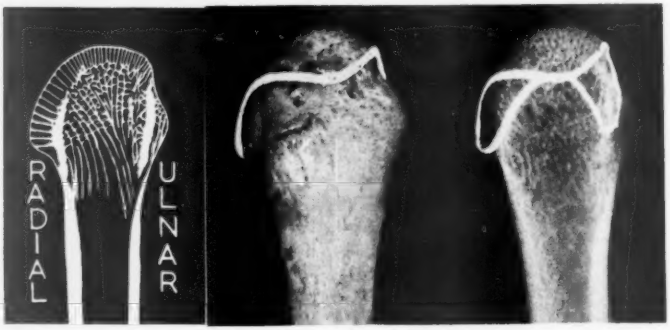


Fig. 1.—A, drawing of radiograph of normal metacarpal showing trabecular pattern, longitudinal condensations and cortex. B, photograph of dorsal aspect of metacarpal with lead foil strip marking synovial attachment. C, radiograph of specimen shown in B.

The rheumatic diseases are manifested radiographically by bone destruction and bone formation, and by the resultant of these two when both are present. The early lesions of rheumatoid arthritis have been described by Fletcher and Rowley (1952) and others. The changes described here have been observed in patients studied chronologically using routine radiography.

Early trabecular loss (Fig. 2). — Destruction often begins as an alteration of trabecular pattern, which may be hazy, thinned, undermined, or thinned-out. So-called juxta-articular porosis is an example of these lesions occurring over a wide area.

Cortical loss and erosion (Fig. 3).—Gross local loss, called erosion and usually involving the

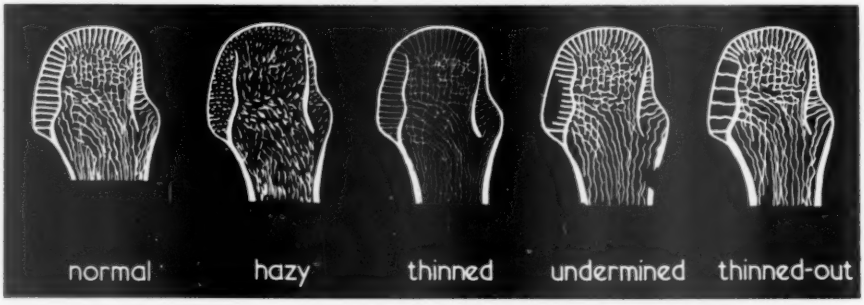


Fig. 2.—Early trabecular loss.

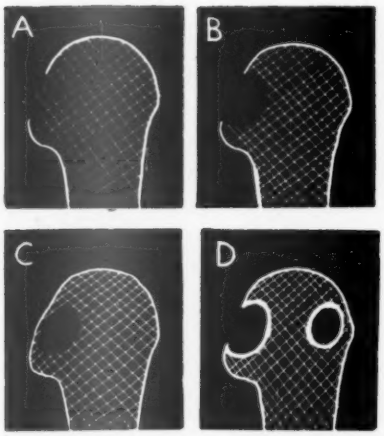


FIG. 3.—Early cortical loss and erosion. A, surface erosion (including cortical "splitting" and "dot and dash" pattern of Fletcher and Rowley). B, pocket erosion. C, enclosed erosion. D, limited erosions.

cortex, may affect only the cortex as a surface erosion, cortex and trabeculæ as a pocket, or apparently lie deeply, being enclosed. Erosions may be limited by coarse new bone, otherwise the bared trabeculæ have a fluffy edge.

New bone formation in head of metacarpal (Fig. 4).—New bone formation has a coarse structure, often clearly defined. It does not follow normal trabecular pattern.

In rheumatoid arthritis it limits erosion against the advancing edge of pannus. In gout, new bone may surround the expanding lesion and project beyond the original contour, either as a bubble or as buttressing on either side. In osteo-arthritis new bone forms in continuation with the joint surface (Collins, 1949).

New bone in the shaft.—New bone in the shaft occurs subperiosteally. Its evolution can be followed from a case of ankylosing spondylitis (Fig. 5). First there is a line of less than cortical density, which later becomes consolidated. These changes are accompanied by widening of the medullary cavity. The final result is distortion of the neck. During the apposition of new bone, destruction of trabeculæ within the shaft and

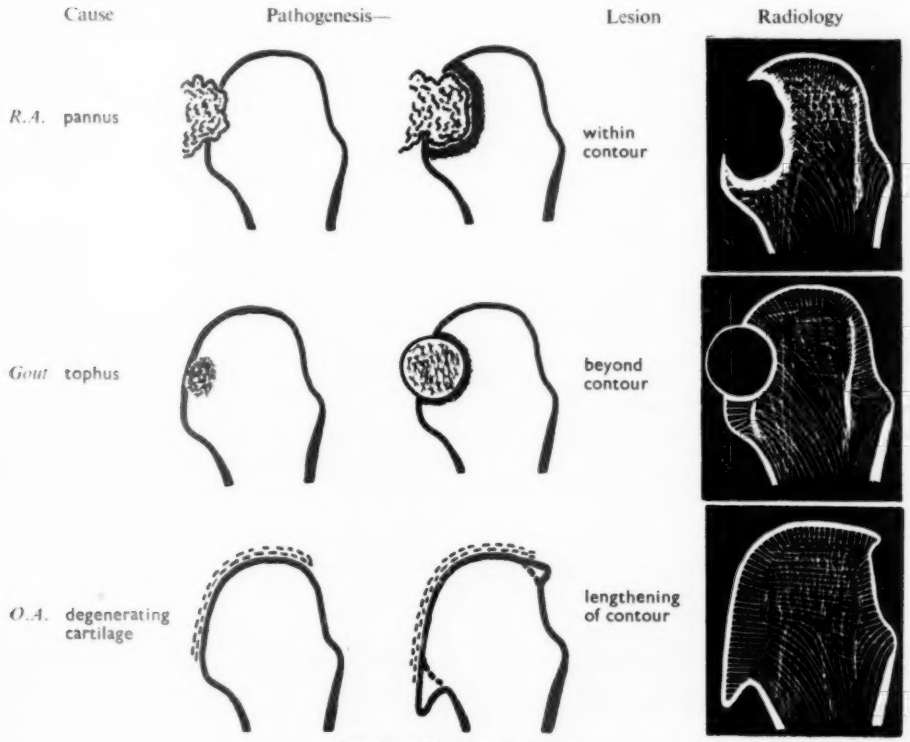
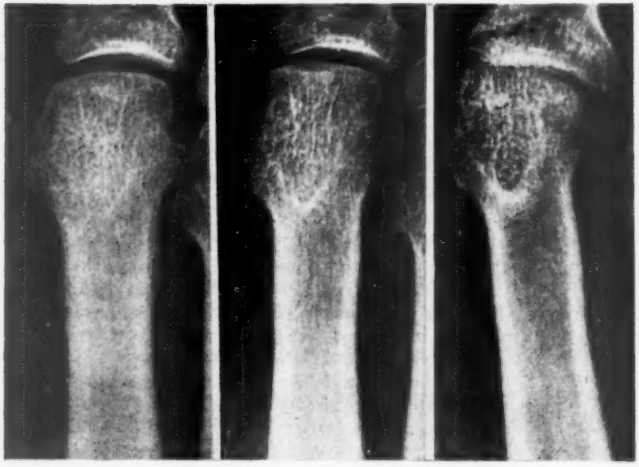


FIG. 4.—New bone formation.



7.12.55 24.7.56 28.8.58

FIG. 5.—Evolution of periosteal new bone in ankylosing spondylitis (*see* text).

FIG. 6.—Lesion occurring a few months after onset of Reiter's disease—periosteal new bone accompanying destruction in proximal phalanx of little toe.

head, and of the articular cortex, occurs. Thus the new bone at the neck suggests destruction within, and may herald articular changes.

The less dense bone is woven bone, which later becomes compact. If the process is slow, as it often is in rheumatoid arthritis, there may be no density change, only the deformity.

Woven subperiosteal bone is more likely to be seen in the following circumstances: (1) When the periosteum would normally be physiologically active in young people—hence its common appearance in bone lesions in children, including Still's disease (Middlemiss, 1951). (2) In diseases having a tendency towards excessive bone production, e.g. Reiter's disease (Fig. 6) (Murray, *et al.*, 1959) and ankylosing spondylitis (Middlemiss, 1956). (3) In hypertrophic osteoarthropathy. (4) When accompanying soft tissue lesions are present, for example, psoriasis and keratodermia blennorrhagica, neurotrophic lesions and in local vascular abnormalities, particularly ischæmia.

Summary.—Density changes alone do not provide reliable criteria of early pathological change in rheumatic diseases which are manifested by bone destruction and/or new bone formation. Early radiographic lesions are described with special reference to the metacarpal.

Acknowledgments.—I wish to thank Mr. Ambrose King and Dr. R. M. Mason for permission to use films of their patients, and Mr. R. F. Ruddick, A.R.P.S., F.I.B.P., for his help in reproducing the illustrations.

REFERENCES

COLLINS, D. H. (1949) The Pathology of Articular and Spinal Disease. London; p. 92.
FLETCHER, D. E., and ROWLEY, K. A. (1952) *Brit. J. Radiol.*, **25**, 282.
MIDDLEMISS, J. H. (1951) *Proc. R. Soc. Med.*, **44**, 805.
—— (1956) *J. Fac. Radiol., Lond.*, **7**, 155.
MURRAY, R. S., OATES, J. K., and YOUNG, A. C. (1958) *J. Fac. Radiol., Lond.*, **9**, 37.

The following paper was also read:

Some Observations on Neuralgic Amyotrophy.—Dr. M. Q. BIRKBECK (Manchester).

Meeting
December 9, 1959

MEETING IN THE DEPARTMENT OF PHYSICAL MEDICINE, HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, LONDON

THE following cases were shown on behalf of Dr. BASIL KIERNANDER, Director of the Department, by Dr. E. D. R. CAMPBELL, Dr. D. Y. MACKENZIE and Dr. THERESE VANIER:

(1) **Arthrogryposis Multiplex Congenita.**
(2) **Dermatomyositis.**
(3) **Diabetes: Goitre: Myasthenia Gravis.**
(4) **Still's Disease.**
(5) **Werdnig-Hoffman Disease.**
(6) **Werdnig-Hoffman Disease (Arrested).**
(7) **Congenital Muscular Dystrophy.**
(8) **Polyneuritis.**
(9) **Asthma.**
(10) **Fibrocystic Disease.**

The antibiotic of choice should be

* *highly effective*
* *well-tolerated*
* *orally administered*
* *non-irritant*

These requirements are well met by

which is of significant value in dealing with

* *Gram-positive cocci, including penicillin-resistant strains of staphylococci*
* *non-specific urethritis*

Tablets and capsules of 250 mg. spiramycin in containers of 20.

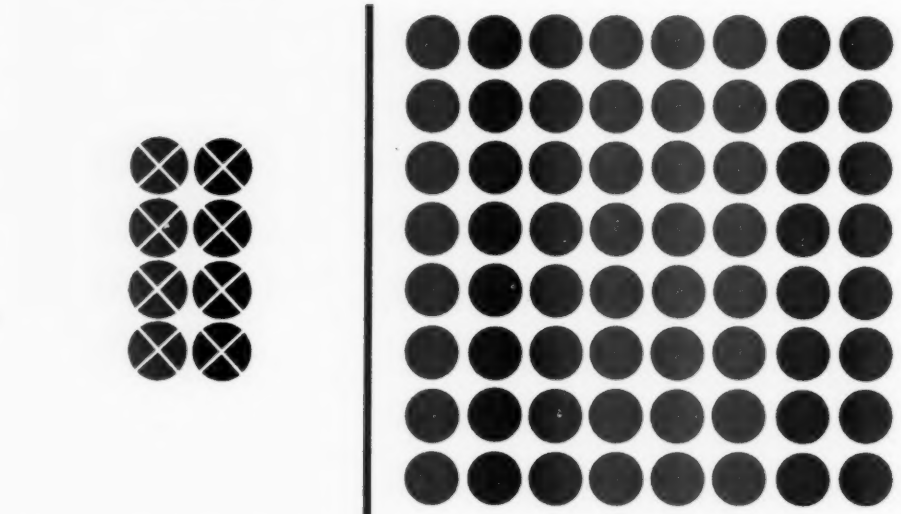
Detailed information is available on request

MANUFACTURED BY MAY & BAKER LTD

An M&B brand Medical Product MA679)

DISTRIBUTORS: PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD • DAGENHAM

SIMPLE SULPHA ARITHMETIC



ONE WEEK'S TREATMENT WITH LEDERKYN **8** TABLETS

ONE WEEK'S TREATMENT WITH OTHER SULPHAS **64** TABLETS

The superiority of LEDERKYN sulphamethoxypyridazine does not rest on dosage alone — the lowest in sulpha drug history. In addition to marked economy and simplification of the therapy, LEDERKYN is longer-acting, better tolerated and has fewer side-effects compared with earlier sulphonamides, Bacteriostatic activity is equal. Safety is based on low required dosage and high solubility. In paediatric practice, LEDERKYN has given good results in a high proportion of infants and children with respiratory infections.

LEDERKYN*

SULPHAMETHOXYPYRIDAZINE

*REGD. TRADEMARK

LEDERKYN TABLETS: *0.5 Gm.*
Bottles of 24, 15/8, 100 £2.18s.8d. and 500 £13.16s.4d.
LEDERKYN PEDRIATIC SUSPENSION: *250 mg./5 cc.*
Bottles of 2 fl. oz. 8/- and 16 fl. oz. £2.16s.8d.

Lederle | CYANAMID

LEDERLE LABORATORIES
a division of
CYANAMID OF GREAT BRITAIN LTD. London W.C.2

Section of General Practice

President—R. J. F. H. PINSENT, M.D.

Meeting
December 16, 1959

DISCUSSION ON CO-OPERATION IN GENERAL PRACTICE

Dr. F. H. Staines (General Practitioner, Callington, Cornwall):

I am a principal in a fully rural National Health Service practice, with a partner. My surgery is five miles from the county boundary between Cornwall and Devon, and one mile from a line dividing the "territories" of two Medical Officers of Health. The practice covers more than 100 square miles, served by 10 District Nurses who are administered by 3 separate health areas. We have between 40 and 50 confinements a year, the majority of which are delivered under our responsibility, either at home, or in Local Authority maternity homes in two counties. There are within the practice area no Local Authority maternity or welfare clinics, other than the School Medical service, though occasional clinics have taken place under the poliomyelitis schemes. So we do all these things for our patients ourselves, running a weekly combined antenatal and immunization clinic, which is enormously assisted by the regular presence of our nearest District Nurse, who is also our Health Visitor, and the occasional presence of her colleagues. The pædiatrician from our nearest Hospital Management Committee has advised additions to the equipment of our nurses and ambulance services, such as low-reading thermometers, phenylketonuria tests and gastric oxygen sets, there being complete freedom of exchange across the county border.

Within my practice area there are no separate Health Visitors, as each of our nurses has her certificate, and combines in one person both functions. It is not surprising that I have no experience of lack of co-operation between Health Visitor and District Nurse.

The enemies of such inter-professional co-operation could be placed in the following order: (1) Empire-building. (2) Lack of subject interest. (3) Lack of information. (4) Overwork.

By "Empire-building" I understand a series of events, first of which is an overgrown sense of personal or professional importance; from which grows not only an excessive valuation of the personal contribution to the business in hand, but also active undervaluation of the contribution of others. This attitude of mind, which amounts to a fundamental defect of character, makes the builder an impossible person with whom to co-operate, because he or she has neither the knowledge nor the desire to work with any other person for any joint purpose. Lack of subject interest includes both the active and the passive phases: both the person who has lost, or never had an interest in his or her job, and the job which has become for some reason uninteresting, perhaps because there is suddenly seen to be no future in it. The person who is bored, fed up, floundering, or disillusioned, is incapable of working actively with other people as he does not even want to work with himself. Under the heading of lack of information comes the impossibility of working with someone of whom you have never heard. It is equally certain that you cannot actively co-operate with someone else unless you know in which direction he is going, you can only passively follow him, like a sheep. True co-operation implies activity not passivity. So, within the limits of our subject, "information" means to me not only the simple knowledge that other services besides one's own exist, but familiarity with those other services' aims, needs and methods and with the people administering them. Lastly, actual or imagined overwork leads to an attitude of mind similar to that described in the old Service expression "D—— you, Jack, I'm all right". The wording goes a little differently, and becomes "D—— your troubles, Jack, I can't worry about them because I have enough of my own".

These are the enemies of co-operation and my suggestions for overcoming them start unfortunately in a negative way. You cannot do very much about empire builders, except either fire them, avoid them, or laugh them off. Lack of interest can be dealt with by encouraging your colleagues in a belief in the value of their work, increasing information, and by making sure that those you employ feel they have some future in their job. Information should never be demanded, especially written information, if this can possibly be avoided. To sit for some hours filling in forms on a subject which is not connected either with one's primary professional skills, or with the well-being of the patient who is one's professional responsibility, breeds a con-

dition of mind which can only be described as "browned off", i.e. antisocial and unco-operative. Every opportunity should be taken to spread information about your side of the joint effort, and to absorb information about the other side. This process is rather like trying to teach a patient the principles of a diabetic diet; it is remembered best if it is done carefully, by small instalments, over a long period. These opportunities are best taken, not made. If you make too many, especially by circulating pieces of paper, you are liable to be mistaken for an empire builder! To avoid overwork is quite simple. Do not overwork yourself or other people and, in particular, never imagine you are overworked, unless you really are.

On the positive side let me define the word "co-operation". It means two or more people working together, not just acting together. The three essential implications about this work are that it is active, that this activity is friendly or happy and that the purpose of the work is for the good of others. In my opinion there are two basic sources of co-operation. I suggest first, the daily use and practice of the basic human decencies and dignities, involving something more than the mere social uses of society. This would include honest endeavour, trust, honour, charity, humility and sympathy. Secondly, I suggest we must each have the interest, wish and desire, to do always the best job possible in the best possible way.

This is where the patient comes in. The patient is the sole cause and purpose of our discussion, and of our being what we are, doctors and nurses. Our job is to keep the patient healthy, by our knowledge, advice and example. Next, to prevent him getting ill, by our laws and regulations, by our watch over his environment and over what he inspires and ingests, by our specific inoculations, and all our other daily measures. And if we can neither keep him healthy, nor prevent him getting ill, we are here to support him in his illness, by the skills of our hands and our brains, and with the drugs that other hands and brains have given us. During that support, we must try to cure his disease. And if we cannot cure his disease, we must, if he lives, teach him to "live with" the disabilities that his disease has forced upon him; and if he dies, see that he dies in comfort and hope. None of us can attempt this task even for one single patient, without help from others. And if we all practise the basic human decencies, and all try honestly to do the best job for the patient, then we must co-operate because each one of us is merely a part of the patient's need.

My suggestion is to extend to all the levels and to all the skills in the Health Services, under whatever authority they come, the principles and traditions of the specialist consultation. If I have a difficult abdominal problem I call in a colleague with specialized knowledge and experience. We examine the patient together, and then "consult". This consultation, as equals in different spheres, results in both of us modifying each other's opinions, and we emerge with an agreed plan for the patient's welfare. Whichever of us has the appropriate skill carries out the plan. Now, is there any reason why I should not call in our District Nurse, similarly, when her special skill bears on the problem? And could not our Health Visitor call in the district M.O.H. "in consultation" and not as a servant summoning the mæstro? If this principle of consultation could be extended between all the medical workers considered here, then bad co-operation between the various facets of the Health Services would be a thing of the past. The ultimate benefit would be not only to all of us, but especially to our patients, whom we all exist to serve.

Miss L. Joan Gray (General Superintendent, Queen's Institute of District Nursing, London):

The definition of co-operation is working together for the same ends and, however good one's intentions, no amount of co-operation will avail unless one really knows the person or persons with whom one hopes to co-operate. By that I mean not only knowing them personally but also knowing and appreciating the contribution each can make for the common good. Whatever our views on the National Health Service when it first came into being, it certainly has resulted in closer integration of the various medical, nursing, hospital and public health services, and I feel certain that all members of the public health team have a greater respect for each other's work than was evident in former years. Although we were all working with the one aim in view, that is the health and welfare of the family, we were constantly being accused of working in watertight compartments, and rightly so.

There are over 10,000 District Nurses in Great Britain and between 6,000 and 7,000 of these are not only State-Registered Nurses but have also taken District Nurse training in addition. Thus they are equipped for all that is required of them, not only as bedside nurses in homes of all types, but they are also enabled to deal with the various social conditions they meet. In the very rural areas, the District Nurse/Midwife is also a qualified Health Visitor and provides a generalized service undertaking district nursing, midwifery and health visiting. For the past hundred years,

since district nursing began, she has worked almost entirely under the direction of a general practitioner and her work has been complementary to his. I think it is true to say that perhaps the greatest co-operation is evident here, but even so, co-operation could be better.

Some general practitioners actually visit homes regularly for no other reason than to give intramuscular and hypodermic injections although a nurse is available and has the equipment to do it, and this appears to be a great waste of the general practitioner's time. It is a very different matter where a doctor pays a first visit late at night and has the drug with him. The family doctor and the District Nurse are very busy people and although it is highly desirable, with all the will in the world it is not always possible for them to meet, but the District Nurse can be of great help to the general practitioner wherever this can be arranged, preferably at the patient's house. In the case of an extensive dressing it is obviously to the benefit of the patient, nurse and doctor if he can visit when the nurse is likely to be at the house. The majority of District Nurses leave a report in each house with the relatives, not only recording all drugs given to the patient, which should be done from the legal aspect, but also to give a full report to the general practitioner or to note any unusual signs and symptoms. These official message papers have proved invaluable and are convenient for the doctor, who may otherwise leave a message as to treatment to be given on a scrap of paper or may leave verbal directions with the relatives, which is not only dangerous but irritating for the nurse.

Many District Nurses call at the doctor's surgery to discuss patients and in some areas the medical group sets aside a short time each day for discussions with the nurse on the condition of the patients and on various social factors which are likely to affect the progress and treatment. A District Nurse appreciates these opportunities as they stimulate her interest.

Drugs are another problem. It is not generally realized that a District Nurse is acting illegally if she gives a drug on a verbal instruction from a doctor, neither has she legal cover when collecting a dangerous drug from a doctor's surgery.

In 1948, for the first time, the District Nurses came into close contact and began to know the Medical Officer of Health of the Local Authority, and in most parts of the country the Medical Officers appreciate the importance of staff meetings, local refresher courses and in-service training, all of which the public health staff enjoy and value greatly.

Members of the health team who have tended to come closer together since 1948 are the District Nurse and the Health Visitor, and there is now a far greater appreciation of each other's work. They should make a point of meeting regularly to discuss families where both are attending (or where there is likely to be a need of both) to decide where their individual duties lie, to prevent overlapping and wastage of time. This teamwork is very important, especially in the care of old people. In a few areas a special geriatric Health Visitor or District Nurse is employed. The Health Visitor and District Nurse/midwife should work together in antenatal and mothercraft classes, each contributing her expert knowledge. Wherever possible the midwife should pay the final visit of the puerperium to the new mother together with the Health Visitor, particularly if the Health Visitor has not seen the mother during the ante-natal period.

I feel that an essential part of any Health Centre should be an office or staffroom where all can meet for coffee or tea or discussions, and where general practitioners, medical officers, hospital staff and students may come together. In some areas members of the British Medical Association invite District Nurses and Health Visitors to their lectures, which is much appreciated, and in another a general practitioner has from time to time invited medical students at the weekend when he arranges for them to meet the Health Visitors, District Nurses and midwives.

In a co-operative society the profits are shared as dividend among the customers. The patient and family are our customers and they certainly reap dividends from a united co-operative team.

Miss Ann A. Graham (Principal Nursing Officer, Northumberland):

Much has been said lately about co-operation between general practitioners and Health Visitors and it has been the subject of numerous conferences and reports. To me it seems such a simple matter, that complicated administrative planning and top level discussion are not really necessary for its achievement.

When I was a newly qualified Health Visitor there was a national diphtheria immunization drive and it was an urgent matter to get the children immunized. In one particular area the doctor's surgery was the only practical place where this could be done. I discussed the situation with the doctor and we decided that special sessions would be necessary to cope with the numbers and it was arranged that I should attend the surgery to work with him. I regarded it all as the normal pattern of my work and as a Nursing Administrator I have always encouraged this freedom of action in my staff. I agree that particularly before the National Health Service Act

this was not the general pattern of relationships between Health Visitors and general practitioners. There was, in fact, definite antagonism in some instances, but this surely is a matter of personalities. The achievement of co-operation lies within people themselves, in their recognition of the advantages of working together and in their sincere desire to help each other for the benefit of the families with whom they are concerned.

The doctor's role is much more generally accepted and understood. He is dealing largely with fundamental, personal and family problems, which produce evidence of physical or mental illness or both. A large proportion of his patients will be suffering from illness in which social and emotional factors play a part. Low standards of hygiene, personal anxieties and disturbed relationships frequently underlie the evidence of bronchial and gastric trouble, headaches, and backaches, with which the doctor is dealing in his surgery. The Health Visitor in the home deals with these underlying problems by educating the families in healthier ways of living, by giving or arranging for practical help where needed and by listening to people talking about their difficulties. The treatment of causes and effects of illness could be more effectively synchronized by a true working partnership between the general practitioner and the Health Visitor. The doctor is accustomed to call in the District Nurse when some physical condition needs her skilled attention—a dressing to be applied or an injection or enema given. Can we hope that in the future, he may immediately think of the Health Visitor when a patient needs reassurance or support in an anxiety condition or explanation and help in carrying out the doctor's instructions? There must surely be few areas nowadays where the general practitioner and Health Visitor do not at least know each other. In my county, the Medical Officer of Health notifies all the general practitioners when a new Health Visitor is appointed to an area, making the initial introduction easier for both.

What then are the reasons why good relationships do not always develop? It may be that previous antagonisms have not been resolved, or there is a lack of complete understanding or appreciation of how a working co-operation could be developed. Where personal conduct is questioned, a talk with the person concerned should be the first procedure. I have always found that on the few occasions when general practitioners have telephoned me to report some action of a Health Visitor, the quickest way to resolve the misunderstanding is to tell the general practitioner that I will ask the Health Visitor to call and see him.

It has been suggested that one of the obstacles to working more closely together is that Health Visitors work in certain defined areas, which do not coincide with the doctor's practice. With a little more imaginative planning and freedom of action on the part of the Health Visitors, I see no reason why this difficulty could not be overcome, at least in special cases. Personal antagonisms have unfortunately sometimes proved to be a bar to co-operation, but after all, very few people can choose with whom they wish to work. As mature people, we ought not to allow these personal feelings to interfere with our work relationships and a little quiet, unemotional thinking will often make us realize that personal dislikes can be overcome when our main concern is providing the best possible service to families. The question of family confidences inevitably arises but I feel sure that when a doctor and Health Visitor are known by the family to be working in liaison with each other, the people themselves are happy to talk to them both and the question of betrayal of confidence does not arise.

Co-operation is undoubtedly improved when the general practitioner works in the Local Authority clinics. When the Maternity Services Committee recommendations are implemented, we may hope for a further development of co-operation, particularly in the care of the expectant mother. The Health Visitor's role in this field is certainly an educational one. The ante-natal period is perhaps the most receptive of all and it is then that the importance of the right maternal attitudes should be taught and the fundamental principles of mental hygiene explained. Our hope for the future is to ensure to the children of the next generation the right emotional climate in which to develop a stable and healthy personality. I see no reason why the Health Visitor should not take part in the ante-natal education of all expectant mothers, whether or not they attend the Local Authority clinic. Health Visitors would, I am sure, welcome to their classes expectant mothers who attend the doctor's surgery for ante-natal care.

Another field in which co-operation could be most valuable, is research. Factual assessment of the value of new ideas and treatment will continue to be necessary and both doctors and Health Visitors working in normal homes are in a unique position to undertake these projects.

Co-operation generally will be furthered by joint meetings of our professional organizations when subjects of common interest can be discussed. These meetings at local level have been very successful and I look forward to a growing appreciation of their value.

Dr. J. E. Haine (Medical Officer of Health, Guildford):

The desirability of close co-operation between the Medical Officer of Health and the general practitioner is obvious, and becoming more evident. Each can help the other by recognizing their individual spheres and working towards the same end. The welfare of patients and of the general public is the aim of us all. The Medical Officer of Health has been pushed farther from clinical work by, in particular, the National Health Service Act, but he is still practising medicine just as is the general practitioner. I speak as Medical Officer of Health of three Districts covering a great deal of the rural part of Surrey. I do not try to cover the County Council or Local Health Authority aspects, though obviously the same principles will apply.

First and foremost the Medical Officer of Health must keep on terms of friendship with general practitioners and appreciate their difficulties, especially, perhaps, their lack of time and clerical assistance when professional calls on them are most numerous. Details of ordinary and professional courtesy must be scrupulously observed at all times. Such details are the prompt and regular payment of fees for notification of infectious diseases and the various vaccination procedures without waiting for a demand, prompt and detailed answers to enquiries, provision of addressed reply-paid envelopes and so on. Existing necessary contact between Medical Officer of Health and general practitioner is mostly restricted to notifications of infectious diseases and records of immunization. However, these do establish contact which ought to lead to co-operation. Discussion and agreement over control measures for infectious diseases are usually very helpful. This is particularly important in residential institutions, and the number of institutions such as schools, nurseries and homes for the aged and other special groups seems to increase every day. When infectious disease occurs it is best to discuss the problem with the practitioner concerned and agree on measures for its control. The general practitioner has the greater experience in the treatment of individual cases; the Medical Officer of Health has greater knowledge of measures for preventing spread, and usually has the latest information from the bacteriological side. He should be in constant close touch with the bacteriologist.

The Medical Officer of Health has clerical and other staff to help him, whilst the general practioner is often alone or at best shares a secretary. Prompt replies by the Medical Officer of Health should be expected to any enquiries that are made, and the Medical Officer of Health should remember that the general practitioner may well be overwhelmed with work, sometimes even forgetting to notify the occasional infectious case. He seldom forgets the really serious or important case where action by the Medical Officer of Health is required, but a telephone call usually clears things up immediately. I supply a weekly bulletin of information on infectious disease notifications to the hundred or so practitioners in my "parish", to hospitals and to others concerned. This merely shows what infections have occurred in the locality, and whether they are isolated cases or widespread epidemics. This bulletin also serves to give items of information from time to time: Ministry advice on immunization procedures, visits of mobile X-ray units and any other item of general or of local interest. I also distribute forms for the unofficial notification of infectious or other cases not ordinarily notifiable. These have proved most useful, and often bring to light occurrences of considerable interest. They also keep me informed of health conditions in a way that even School Absence reports cannot do. The forms are, of course, pre-addressed and franked.

This procedure leads to more frequent exchange of views with my colleagues in general practice, and discussions on unusual or interesting cases. For example, frequent infections of *Salmonella typhimurium* and of Sonne dysentery cause a great deal of "nuisance" in my area. They are occasionally of serious importance, as when food handlers and children's nurses are concerned. The need for co-operation between Medical Officer of Health and general practitioner in such cases is obvious, and always helpful.

I am perhaps fortunate in having a visiting nurse under my personal direction. She is a health visitor of a kind, though not so designated. She makes the usual routine enquiries in cases of infectious disease instead of the Public Health Inspector, as is more usual, and she is also available to take swabs or other pathological specimens as required. This is a service that obviously saves the general practitioner visits and time, especially when specimens have to be taken repeatedly from the same patient. However, he must be kept fully informed. In a large rural area this is a most valuable service. The nurse also visits most tuberculosis cases, mainly over housing matters, and many old persons in any kind of need. Wherever action of any kind is contemplated, there is discussion with the private doctor and housing, home help, extra nourish-

ment and many other arrangements are provided as a result. It is to the aged in particular, no doubt, that help is most often taken.

Now, almost needless to say, the initiative is as often as not taken by the doctor in approaching the Medical Officer of Health for help. Nuisances and unhygienic conditions are frequently brought to light that would otherwise pass unnoticed. These discussions, too, lead to enquiries about all sorts of other matters, and encourage co-operation in the widest possible way. The Medical Officer of Health is in a position to represent the needs of particular patients to the local authority or voluntary body who can best help. He is also in a position to interpret, in simple language, medical problems or requirements to his authority. I think this type of co-operation is likely to increase. Not only are the aged receiving more consideration and help, but special facilities formerly available particularly to tuberculous families are now being extended to all forms of chest and heart disease. The Chest and Heart Association, formerly the National Association for the Prevention of Tuberculosis, has shown the way ahead on this extension of "social medicine".

The outlook for the future is, as I see it, for closer and closer relations between the two types of medical service: the work of the private doctor in caring for his patients being supplemented by the social care available through the services of the Medical Officer of Health.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Browning (E.). Harmful effects of ionising radiations. pp. 158. Amsterdam: Elsevier. 18s. 1959.

Carcassi (U.). Eritroenzimopatie ed anemie emolitiche. pp. 376. Pisa: Omnia Medica. 1959.

Guthrie (D. J.). The Royal Edinburgh Hospital for Sick Children. pp. 75. Edinburgh and London: Livingstone. 17s. 6d. 1960.

Haynes (B. G.). Autonomic dyspraxia: an hypothesis for the mechanism of psychosis, neurosis and psychosomatic disease. pp. 122. London: Lewis. 15s. 1958.

Kiss (F.), and **Tarjan (G.).** Hirnkreislauf und Schwangerschaftstoxikose. pp. 132. Leipzig: Barth. 1959.

LeFanu (W. R.). A catalogue of the portraits and other paintings, drawings and sculpture in the Royal College of Surgeons of England. pp. 119+52. Edinburgh and London: Livingstone. 30s. 1960.

Loewenstein (J.). The treatment of impotence. pp. 48. London: Hamilton. 1947.

Lucas (R. B.), and **Kramer (I. R. H.).** Bacteriology for students of dental surgery. 2nd ed. pp. 288. London: Churchill. 27s. 6d. 1959.

McDonagh (J. E. R.). A final study in the nature of disease. pp. 376. London: Heinemann. 30s. 1959.

Marti-Ibanez (F.). Men, moulds and history. pp. 114. New York: MD Publications. 1958.

Pasteur (L.). Études sur la bière. pp. 387. Paris: Gauthier-Villars. 1876.

Pattison (F. L. M.). Toxic aliphatic fluorine compounds. pp. 227. Amsterdam: Elsevier. 18s. 1959.

Roumania: Ministry of Health and Social Welfare. Health protection in the Rumanian's People's Republic. Bucharest. 1959.

Savill (A. F.). Alexander the Great and his time. 3rd ed. pp. 302. London: Barrie and Rockliff. 18s. 1959.

Shaw (R. R.), and **Paulson (D. L.).** The treatment of bronchial neoplasms. pp. 135. Springfield, Ill.: Thomas. 64s. 1959.

Smirk (F. H.). High arterial pressure. pp. 674. Oxford: Blackwell. 75s. 1957.

Squibb Institute for Medical Research. The centennial lectures commemorating the one hundredth anniversary of E. R. Squibb and Sons. Edited by James T. Culbertson. pp. 292. New York: Putnam. 1959.

Steendijk (R.). Skeletal calcification and phosphate metabolism. pp. 174. Amsterdam: Ruysendaal. 1959.

Stringa (G.). Trapianti ossie autoplastici nell'uomo. pp. 200. Florence: Istituto Ortopedico Toscano. 1959.

Taylor (H. B.). Medical radiesthesia pp. 106. London: Greaves. 10s. 6d. 1959.

Teicher (H.). Das Sternalmark. pp. 124. Leipzig: Thieme. 1958.

Vallery-Radot (P.-R.). Médicine a l'échelle humaine. pp. 186. Paris: Fayard. Frs. 750. 1959.

Vanghetti (G.). Vitalizzazione delle membra artificiali. pp. 225. Milan: Hoepli. 1916.

Vasconcelos (E.). Modern methods of amputation. pp. 253. New York: Philosophical Library. 1945.

Weber (F. Parkes). Miscellaneous notes. (Fourth and Fifth series.) London: Lewis. 1960.

"In general practice at least

40% of patients have symptoms

of functional disorder..."

Lancet (1958) **1**, 525

Bellergal Retard

BY **SANDOZ**

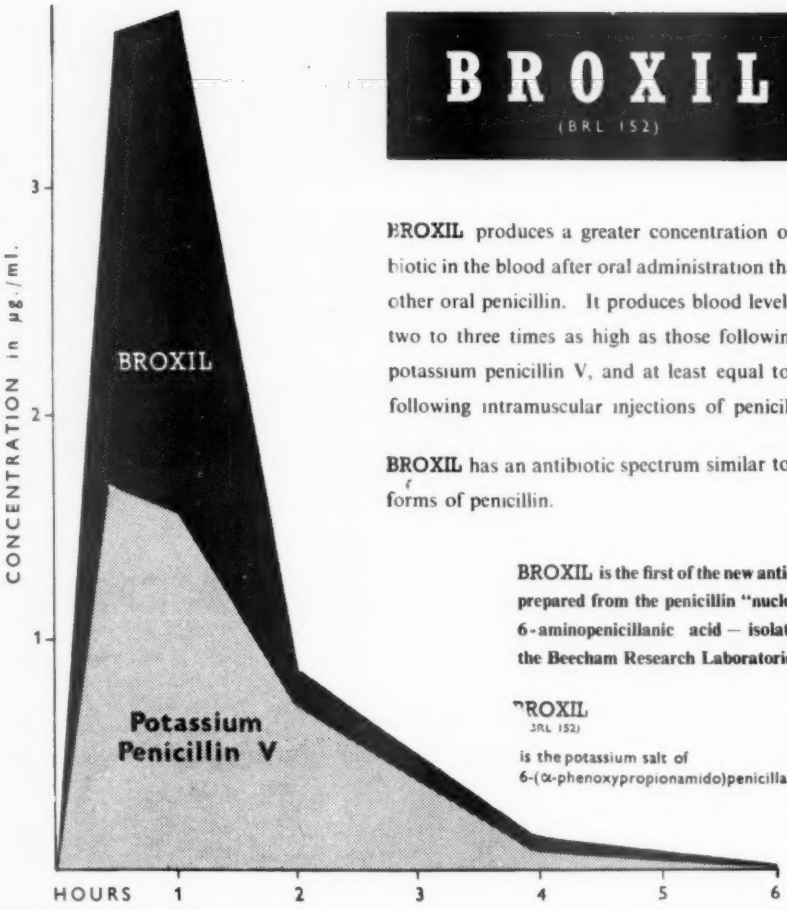
in functional disorders

1 tablet night and morning for **continuous** control of symptoms

0.2 mg. total alkaloids of belladonna
0.6 mg. Ergotamine Tartrate B.P.
40 mg. Phenobarbitone B.P.

Sandoz House **23 Great Castle Street** **London, W.1**

the HIGH PEAK oral penicillin



BROXIL
(BRL 152)

BROXIL produces a greater concentration of antibiotic in the blood after oral administration than any other oral penicillin. It produces blood level peaks two to three times as high as those following oral potassium penicillin V, and at least equal to those following intramuscular injections of penicillin G

BROXIL has an antibiotic spectrum similar to other forms of penicillin.

BROXIL is the first of the new antibiotics prepared from the penicillin "nucleus" – 6-aminopenicillanic acid – isolated in the Beecham Research Laboratories.

BROXIL
(BRL 152)
is the potassium salt of
6-(α-phenoxypropionamido)penicillanic acid

BEECHAM RESEARCH
Laboratories Ltd.
BRENTFORD, MIDDLESEX
Tel.: ISLeworth 4111

AVAILABILITY

Vials of 12 tablets.
Basic N.H.S. price: 125 mg. 8/-, 250 mg. 14/9d.

Bottles of 100 tablets.
Basic N.H.S. price: 125 mg. 54/9d., 250 mg. 108/-.

Section of Endocrinology

President—Professor F. T. G. PRUNTY, M.D., F.R.C.P.

Meeting
November 25, 1959

Two Cases of Endocrine Disease Presenting as Psychiatric Problems.—RICHARD ASHER, M.D.

I.—*Islet Cell Tumour, Presenting as Hysteria*

Mrs. E. P., a housewife aged 47, was referred to the Central Middlesex Hospital in July 1959 with a request for treatment by hypnosis because for five years she had had convulsions, which were occurring twice daily, had been investigated at several hospitals and had not responded to psychiatric treatment. She could give little account of her attacks, but her daughter said the convulsions were preceded by pallor and shouting. She had no abnormal physical signs, and a trial of anticonvulsant drugs did not reduce the frequency or duration of the attacks. She was, therefore, admitted to hospital for observation. She continued to have one or two attacks daily and it was found that 50% glucose produced rapid return of consciousness. Further study showed that during the attacks the blood sugar was invariably low (30 to 40 mg/100 ml) and that glucose always restored normality.

Starvation for twenty-four hours did not provoke an attack, and a glucose tolerance test continued for nine hours was normal, findings which had been reported in other cases of endogenous hyperinsulinism and which may confuse the diagnosis (Garland, 1958, *Proc. R. Soc. Med.*, **51**, 979.). No clear relationship to meals existed; she did not sweat in all attacks (although profusely in some), and she never complained of hunger.

The pancreas was explored by Mr. W. P. Gummer, and a cherry-sized adenoma enucleated from the upper border of the pancreas at the junction of the neck and the body. Subsequently the patient has had no more attacks and is in good health.

The important features of this case were the close resemblance of hypoglycæmic to hysterical behaviour, the normal glucose tolerance test, and the failure of starvation to produce an attack.

Professor Russell Fraser: Spontaneous hypoglycæmia due to an islet cell tumour is often very difficult to demonstrate, unless an attack can be observed. For this we have found no help from the glucose tolerance test, but have found two procedures to be very helpful when the twelve-hour fasting blood sugar is normal: (*a*) A forty-eight-hour fasting blood sugar (any lesser period being unreliable). (*b*) Insulin tolerance tests using the standard dose of 0·1 unit/kg or 3·7 units/sq. m. In the latter there is a slow return from hypoglycæmia in these cases, and the hypoglycæmic responsiveness index or the sum of the absolute blood sugar values at 60, 90 and 120 minutes is below the normal value of 150 to 180; an attack may be produced. This test is performed as for Simmond's disease (Fraser, 1955, *Med. Pr.*, **234**, 389) and is free from hazard if three-hourly meals are ensured for the rest of the day. 50 mg cortisone is also given at the end of the test if the hypoglycæmia has been severe.

II.—*Panhypopituitarism Referred to the Psychiatric Department*

A. J., aged 46, a railway clerk complaining of depression, weakness and impotence, was referred to the psychiatric department at the Central Middlesex Hospital, but himself insisted on being seen by an endocrinologist because he had been told in 1947 that he had a pituitary tumour. This had been discovered when his skull was X-rayed after a fall.

As a youth he was athletic, highly and actively sexual and very hairy. When he was 19 years old, working on the railway, a train ran over both his feet removing all his toes. Thereafter he became progressively weaker, his potency waned till he was impotent and he lost most of his facial and pubic hair.

In 1954 he complained that his workmates were mocking him, that he felt constantly tired and was contemplating suicide. He also complained of excessive thirst and passing 15–20 pints urine per twenty-four hours for the last twenty years. On examination he had the typical appearances of a eunuch. X-ray of the skull

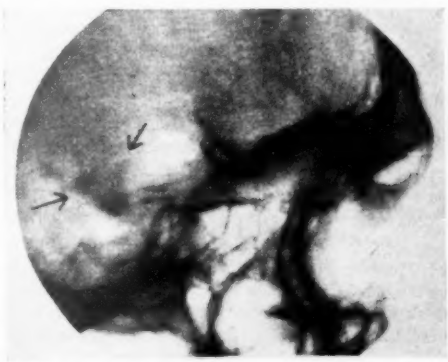


FIG. 1.—The calcified suprasellar tumour (arrowed),

(Fig. 1) showed a large calcified suprasellar tumour with erosion of the posterior clinoid processes and some enlargement of the sella. 17-ketosteroid excretion was 3·3 mg/24 hours. The resting plasma 17-hydroxycorticosteroid level was zero, rising after a four-hour infusion of ACTH to 14 μg/100 ml. This was a subnormal response. Glucose tolerance test normal. Vasopressin tannate in oil corrected his diabetes insipidus ig. 2).

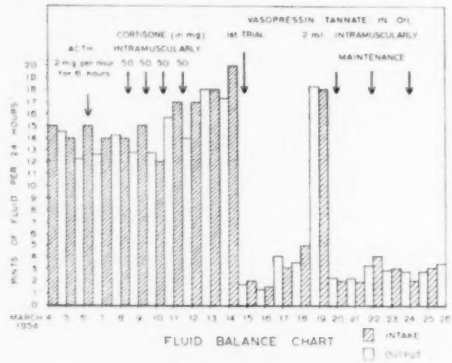


FIG. 2.—Response to vasopressin.

A diagnosis of panhypopituitarism and diabetes insipidus due to a suprasellar tumour was made. He was treated with cortisone, thyroid, testosterone and vasopressin, and has been maintained on these for the last five years. The response to treatment was immediate. His potency returned and he began to have frequent sexual intercourse. His paranoid attitude depression and timid drooping mien all disappeared and he has continued in good physical and mental health.

Dr. O. Garrod: The fact that severe diabetes insipidus persisted in this case shows that a fair degree of anterior pituitary corticotrophic function must have been present. Gonadal function is almost invariably the first to fail, and is often present without evidence of significant thyroid or adrenal failure, in hypopituitarism. The term panhypopituitarism is best confined to those cases in which all the adenohypophyseal functions have failed, regardless of whether neurohypophyseal function is affected.

Primary Myxœdema with Severe Cardiac Involvement, Masquerading Initially as Hypopituitary Myxœdema.—OLIVER GARROD, M.D.

Mrs. N. B., aged 50, housewife, admitted to hospital on 19.2.59 in a state of extreme weakness.

History.—1932: Severe post-partum hæmorrhage complicated by peritonitis and failure of lactation; periods returned after two months. 1936: Second post-partum hæmorrhage with failure of lactation and subsequent return of periods. Never quite well since then. Treated periodically for backache, "anæmia", and "neurosis". Pubic hair never regrew after operation for uterine prolapse in 1942. For three years there was increasing weakness, sensitivity to cold, tendency to faint, menorrhagia, gradual onset of deafness and dryness of skin and hair. In August 1958 dysarthria and bilateral nerve deafness were noted. Periods ceased a few months before admission.

On examination.—Very pale and myxœdematous; drowsy and lethargic; croaky dysarthria; weight 112 lb; height 5 ft 2 in.; absence of axillary and pubic hair, and of body and areolar pigmentation. Thyroid gland not palpable; pulse 80 regular; blood pressure 140/90; heart grossly enlarged; left lung base congested; jugular venous pressure not raised; no œdema; myotonic ankle-jerks; urinalysis negative.

Preliminary investigations.—Hæmoglobin 85%; W.B.C. 5,050; serum cholesterol 360, fasting blood sugar 75 mg/100 ml; serum Na 128, K 5·5, Cl 90 mEq/l; blood urea 81 mg/100 ml; urinary 17-ketosteroids 0·7, 17-ketogenic steroids 7 mg/twenty-four hours; B.M.R. −43% (Robertson and Reid); ECG generalized very low voltage; chest X-ray showed gross cardiomegaly (Fig. 1).

Treatment and progress.—Initially, in view of the history and clinical findings, a diagnosis of hypopituitary myxœdema was made and treatment was started with thyroid extract 30 mg and oral cortisone 25 mg/day. After one week, the dose of thyroid extract was increased to 60 mg/day. The patient remained weak and drowsy, with frequent nausea, occasional vomiting and slight pyrexia, and went into congestive heart failure ten days after starting treatment. Further chest X-rays suggested pericardial effusion and small left basal effusion. She was put on digitalis and chlorothiazide, and cortisone was increased temporarily to 50 mg/day. Blood pressure rose to 180/110, but was very labile, ranging between 100/60 and 190/110. Five weeks after admission she collapsed (blood pressure 85/55; 6 mm pulsus paradoxus; drowsy and disorientated). For a further month her condition remained precarious, hypertension persisted, ECG voltage and heart size did not decrease, but congestive failure slowly subsided. On 24.4.59 she was put on lævo-thyroxine, 0·15 mg and triiodothyronine 0·02 mg/day, and cortisone was continued at 25 mg/day. Thereafter, her blood pressure remained normal and her condition slowly improved.

Further investigations.—ECG became normal after three to four months, and heart size normal (radiologically) between four and seven months, after starting treatment (Fig. 2).

Radio-iodine tests: (*a*) Before T.S.H.: Forty-

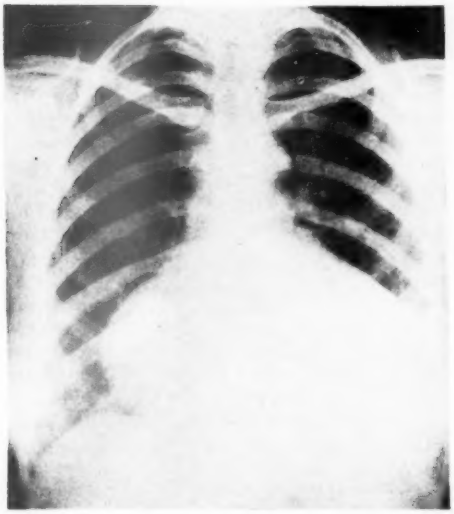


FIG. 1.—Before treatment.

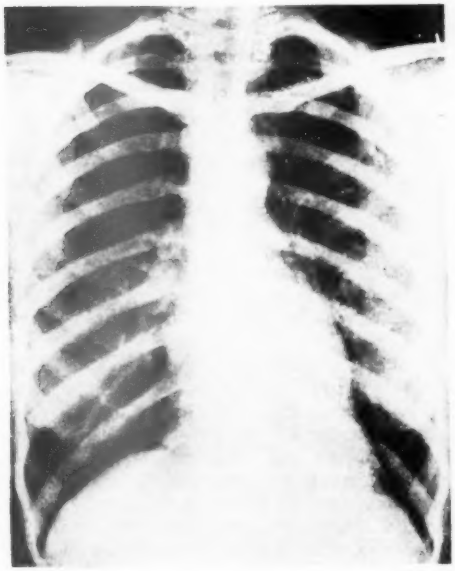


FIG. 2.—Six months after starting treatment.

eight-hour neck uptake 2·5%, urinary excretion 58%; T=1·0. (*b*) After T.S.H. (20 U.S.P. units during two days): Forty-eight-hour neck uptake 8%, urinary excretion 50%; T=2·0.

Thymol turbidity, 4·5 units. Thyroglobulin complement-fixation test weak positive, titre 1 in 4. Tanned red cell agglutination negative. Urinary F.S.H. (after two months' thyroid treatment)=less than 10 units/twenty-four hours.

Subsequent progress.—Steady improvement; weight stabilized at 98 lb, cortisone slowly reduced and stopped on 14.9.59; lævo-thyroxine maintained at 0·2 mg/day. 30.9.59: 17-keto-steroids 1·8, 17-ketogenic steroids 5·5 mg/twenty-four hours. Menses and transient menorrhagia returned in July 1959. Subsequent iron-deficiency anæmia responded to oral ferrous sulphate. She now enjoys normal health.

Conclusions.—Initially, it was impossible to distinguish clinically between primary myxœdema with secondary pituitary failure and hypopituitary myxœdema. The severe cardiac complications favoured primary myxœdema, as did her menstrual history and subsequent progress when cortisone was discontinued. The transient hypertension and possibly the congestive failure, as suggested by Dr. J. D. N. Nabarro, may have been partly caused by retarded cortisone metabolism due to myxœdema; it subsided despite continued administration of this steroid. The failure of response to T.S.H. does not, by itself, preclude the possibility of hypopituitarism, for thyroid function may eventually fail irreversibly in long-standing hypopituitarism (Fraser and Garrod, 1955, *Brit. med. J.*, ii, 1484).

Hyperophthalmic Graves' Disease, with Pituitary Tumour and Hyperparathyroidism.—G. F. JOPLIN, M.R.C.P., M. T. HARRISON, M.D., M.R.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

Mr. J. V., aged 58, was referred to Hammersmith Hospital in July 1958 with severe and increasing exophthalmos present for five months, yet with normal ^{131}I and no symptoms of thyrotoxicosis.

On examination.—Severe proptosis, marked conjunctival congestion and œdema, and corneal ulceration. Marked upper lid bulge. Moderate restriction of movements. Thyroid just palpable. No signs of thyrotoxicosis, and nutrition normal.

Investigations.—Thyroid: ^{131}I tests normal (in Athens). B.M.R. −1%.

Pituitary: Skull X-ray showed uniform expansion of the sella (165 sq. mm—normal being <130 sq. mm) with thinning of the dorsum sellæ (*see* Figs. 1 and 2). Visual fields normal. Augmented insulin tolerance test showed insulin resistance: 0·3 unit S.I./kg body weight given I.V.; sum of blood sugars at 60, 90, and 120 minutes=199 (normal <100).

Parathyroid: Serum Ca 13·8 mg/100 ml, PO_4 2·0 mg/100 ml (mean of 4 readings). Alkaline phosphatase 7 K-A units. Phosphate excretion index = +0·34 and +0·54 (normal = ±0·1). Strontium tracer test (Fraser, Harrison and

FIG. 1.

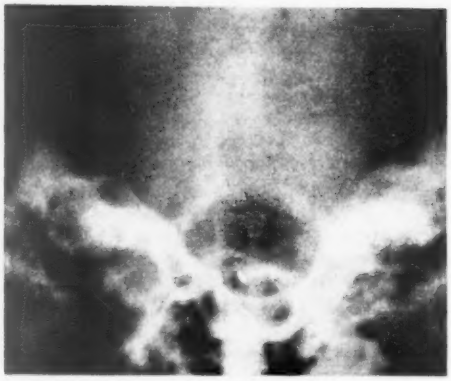


FIG. 2.

FIGS. 1 and 2.—Lateral and 25 degree tilt fronto-occipital skull films to show the 2 seeds of ^{198}Au in the pituitary gland.

Ibbertson, 1960, *Quart. J. Med.*, in press) showed the rate of calcium deposition in bone to be 2·5 plasma units/day (normal = 1–2 p.u./day). X-rays showed no features of hyperparathyroidism.

Adrenal: 17-ketosteroids and 17-ketogenic steroids (on prednisone 5 mg twelve-hourly) = 7·7 and 4·2 mg/twenty-four hours, i.e. no abnormalities.

Treatment.—The severe ocular features were the immediate consideration and so prednisone, thyroxine, diuretics and continuous upright posture were begun forthwith, as well as local eye treatment.

20.7.59: 2 seeds of ^{198}Au (9·5 mc each) were implanted into the pituitary by needle passed transnasally (Figs. 1 and 2). The dose was planned to be well below that which would result in hypopituitarism. By calculation, 90% of the gland received more than 10,000 rads.

Progress.—The infective and congestive eye features rapidly settled following pituitary irradiation, with diminution in proptosis. No further diminution in eye movements occurred. The biochemical abnormalities of hyperparathyroidism have not altered in the four months following pituitary implant. Sexual function has not been impaired, and there were no complications of the pituitary implant.

Comment.—Severe exophthalmos is not infrequent in patients who, like this one, have apparently normal thyroid function. But this patient is unique, as far as we know, in that he also has signs of a pituitary tumour. It may well be that the tumour was secreting excess "exophthalmos-producing substance", and that his case offers further evidence of a pituitary factor in exophthalmos.

Dr. M. Harrison: It is possible that in this patient the hyperparathyroidism, as well as the exophthalmos, is dependent on overproduction of a hormone from the pituitary gland. Recently we have obtained some evidence that growth hormone may have a parathyrotrophic action. Several investigators have reported that hypercalciuria follows the administration of human growth hormone in man. We have found that bovine growth hormone, in a dose of 3 mg/day, similarly produces hypercalciuria in hypophysectomized rats. However, in rats which are both parathyroidectomized and hypophysectomized, no change in urine calcium is seen, although the growth hormone still leads to weight gain. This suggests that one effect of growth hormone is stimulation of the parathyroid glands. The hypercalciuria and osteoporosis of acromegaly may in part be accounted for in this way, as well as the hypercalcæmia and rapid bone deposition in this patient.

Turner's Syndrome with Chromatin-negative Buccal Smears and Ovaries.—C. M. R. KIRKPATRICK, M.B. (for D. FERRIMAN, D.M., M.R.C.P.).

P. P., female, aged 24, admitted 28.8.58 under Mr. K. A. Moore. Marked webbing of neck with low hair-line (Fig. 1). Height 4 ft 6 in. Hypoplastic breasts. Axillary and pubic hair present. Prominent sternum. Menarche at 15 years. Periods regular at monthly intervals with occasional episodes of oligomenorrhœa. Buccal mucosal smears chromatin negative (Dr. I. H. Gordon, confirmed by Dr. P. E. Polani). Ovaries present but small: right $\frac{3}{4} \times \frac{1}{4}$ in., left $1\frac{1}{4} \times \frac{1}{4}$ in. Biopsy (at laparotomy for exploration left ureter) showed ovarian stroma with occasional corpora albicantia but no active follicles (Fig. 2). Steroid excretions (Miss B. E. W. Page): œstriol 3·5 μg, œstrone 2·1 μg, œstradiol none, 17-ketosteroids 4·6 mg/twenty-four hours.

Original admission was for appendicular abscess treated by appendicectomy and drainage (Mr. Marco Caine). Readmission 12.3.59 with

FIG. 1.—Turner's syndrome, showing webbing.

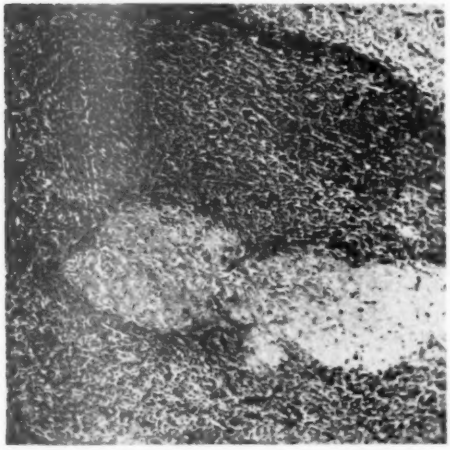


FIG. 2.—Turner's syndrome ovarian section.

left loin pain, fever and pus cells and *Proteus vulgaris* in the urine. Blood urea 38 mg/100 ml. Urea clearance 42% normal.

Further investigation and treatment (Mr. B. H. Page).—Dilated calyces and thinning of renal cortex on both sides, bifid pelvis on the right. Non-specific ureteritis of lower end of left ureter and dilatation above and gross infection of a non-functioning left kidney. Nephrostomy was performed and later allowed to close after return of function and demonstration of passage of urine down left ureter. Urine now sterile. The cæcum was centrally placed, and the appendix was to the left of the mid-line, so that the appendix abscess lay near to the left ureter. It is probable that the renal findings can be accounted for on an acquired basis.

The interest of this case lies in the association of significantly sized ovaries with menstruation in chromatin-negative Turner's syndrome. The chromosomal constitution is presumably XO, though it would be desirable to confirm this; a chromosome count was attempted but failed. Hutchings (1959, *J. clin. Endocrin.*, **19**, 375) reported a dwarfed girl of 13 with chromatin-negative nuclei and significant ovaries.

Cushing's Syndrome with Bilateral Calcification of the Adrenal Glands.—R. R. DE MOWBRAY, D.M., M.R.C.P.

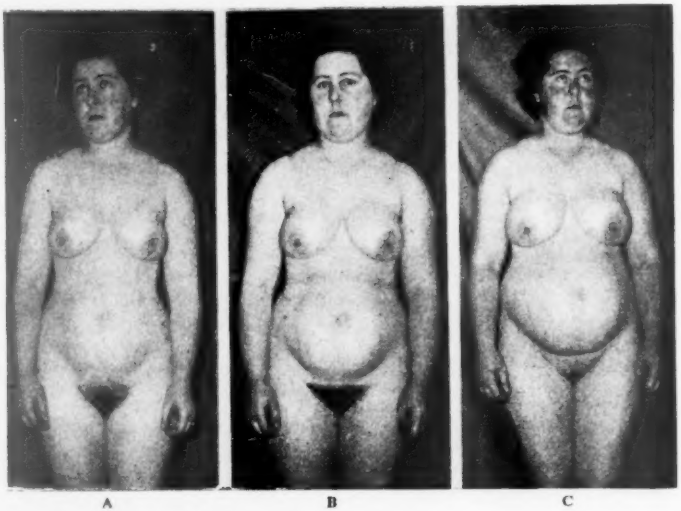
Mrs. J. W., aged 27.

History.—Married at 17 and had 3 children before the age of 21. First child delivered by forceps after trial labour lasting seventeen hours, during which there was fœtal distress and the mother showed signs of exhaustion. Pregnancies and confinements otherwise normal except that lactation failed early on each occasion. After the third confinement she had only two menstrual periods and then developed almost complete amenorrhœa, with increased appetite and progressive gain in weight, reaching 12 st. in August 1958. "Nervous breakdown" with depression in March 1955, with spontaneous recovery. At the same time she developed left-sided frontal headaches and dyspnœa on exertion. During the summer of 1958 she noticed hirsutism on the face and limbs with loss of hair from the head and rounding and blotchiness of the face. No past illnesses of note.

On examination.—10.11.58 (Fig. 1A): Slight generalized obesity. Rounding and plethora of the face. Slight hirsutism of the face and limbs. Pubic hair feminine in distribution. Head hair dry and coarse. No striæ. Blood pressure 155/110. Other systems normal. Gynæcological examination normal.

16.2.59 (Fig. 1B): She had gained more weight, the face had become more rounded and plethoric, striæ appeared over the abdomen and thighs and she complained of backache. Urine contained no sugar or albumin.

Investigations.—*X-rays* showed calcification in both adrenal glands but normal-sized glands after presacral insufflation. Heart shadow slightly enlarged. Lungs clear. No spinal osteoporosis. Urinary 17-ketosteroids 23·8, 17-ketogenic steroids 24·2, 17-hydroxysteroids 32·0 mg/twenty-four hours. B.M.R. —23%. Glucose tolerance normal. Blood urea, serum sodium, potassium, chlorides, calcium and



A B C

FIG. 1.—A, November 1958. B, February 1959, without treatment. C, October 1959, five months after right adrenalectomy.

FIG. 2.—High power view of calcified area of the adrenal gland showing also intracellular deposition of calcium in a hyperplastic zone. × 115.

inorganic phosphate all normal. Blood count normal.

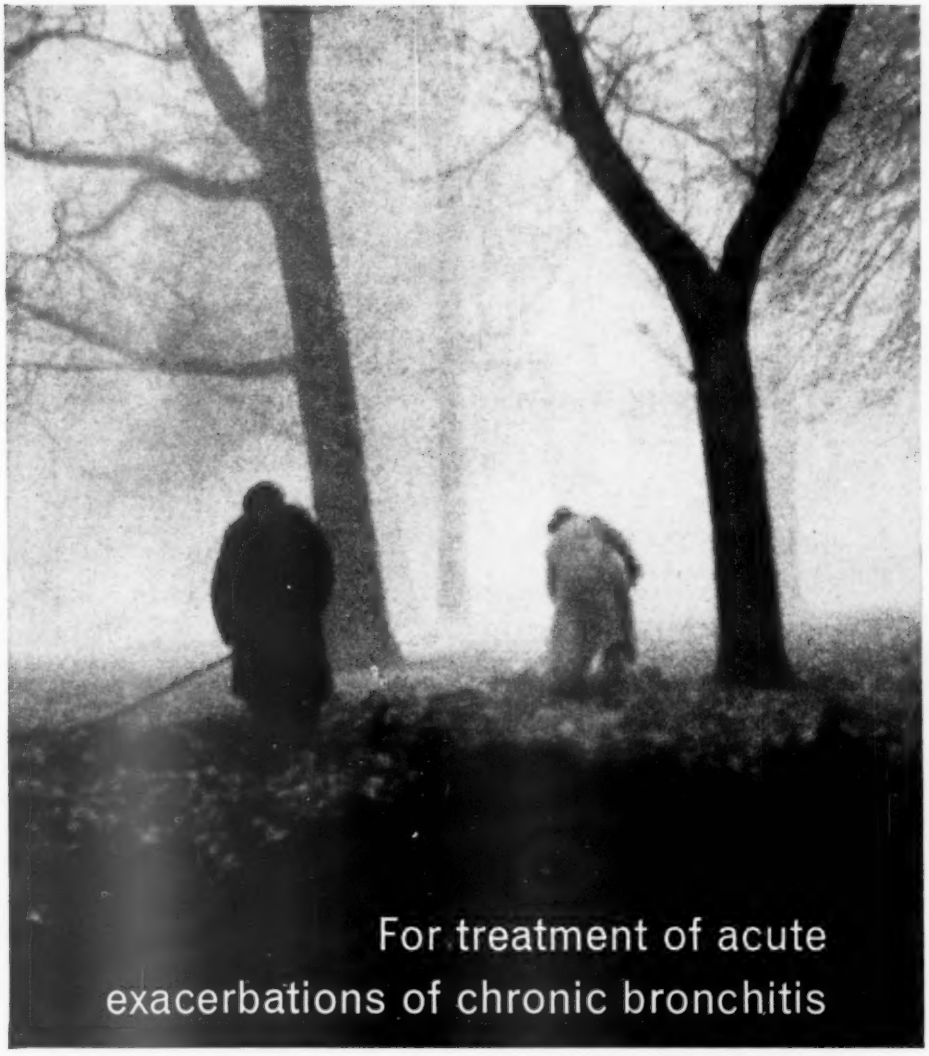
Treatment and progress.—9.5.59: Total right adrenalectomy (Mr. H. A. Small) under cover of intramuscular cortisone and intravenous hydrocortisone. In spite of this the picture of Cushing's syndrome continued to progress. 10.10.59: Total left adrenalectomy (Mr. Small) under steroid cover as before. Since then maintained on cortisone acetate 37·5 mg daily. The features of Cushing's syndrome are slowly regressing.

Comment.—Cushing's syndrome originated in this case after a series of three pregnancies between the ages of 17 and 21 years. The unusual feature was the presence of bilateral adrenal calcification. Histological examination (Fig. 2) showed that both the cortex and medulla were involved; in some areas necrotic adrenal tissue was fibrosed and calcified, resembling bone-formation, and in other areas intracellular deposition of calcium was found in the midst of hyperplastic cortical tissue. There was no evidence of tuberculous infection. The most likely cause of the calcification was thought to be previous hæmorrhage into the glands, possibly in infancy or during pregnancy or labour. Whether partial destruction of the adrenal cortex was a stimulus to increased secretion of corticotrophin and thus an additional stimulus to the development of Cushing's syndrome or whether the two conditions were unrelated is a matter for speculation. In either case pregnancy seems to have been the main causal factor.

Acknowledgments.—I wish to thank Dr. M. S. Ross and Mrs. A. M. Robinson for laboratory investigations, Dr. A. G. Stansfeld for his opinion on the histological material, Dr. A. S. Craner for radiological investigations and Mr. N. K. Harrison and Mr. P. R. Crocker for the photography.

Dr. A. W. Spence asked whether the ovaries had been examined at operation, since Cushing's syndrome might be produced by a tumour of adrenal cortical rests in the ovary.

Dr. de Mowbray, in reply, said that the ovaries were not examined at operation, which was carried out by the lumbar route. She had been examined by a gynæcologist with negative results. The fact that she is improving after adrenalectomy suggests that the condition was due to adrenal hyperplasia.



CHLOROMYCETIN

CHLOROMYCETIN* (chloramphenicol B.P., P.D. & Co.) is presented as
CHLOROMYCETIN Capsules 0.25g.
CHLOROMYCETIN Succinate 1g.
Suspension CHLOROMYCETIN Palmitate 125 mg. per 4 ml.
*Trade Mark

PARKE-DAVIS

PARKE, DAVIS & COMPANY, *Inc. U.S.A. Liability Limited*, Hounslow, Middlesex. Tel.: HOUnslow 2361

A milligram in time . . .

QUICKER relief of migraine with

LESS ergotamine

Cafergot-Q

BY **SANDOZ**

to be chewed for

IMMEDIATE buccal absorption

Each Cafergot-Q tablet contains
1 mg. Ergotamine Tartrate B.P.
100 mg. Caffeine B.P.
in a chocolate-flavoured base

Clinical Section

President—T. C. HUNT, D.M.

Meeting
November 13, 1959

Hæmobilia: a Case with Massive Repeated Bleeding from the Biliary Tract.—OWEN E. OWEN, M.B., F.R.C.S. (for NORMAN C. TANNER, M.D., F.R.C.S.).

The term "traumatic hæmobilia" was suggested by Sandblom (1948) to describe gross hæmorrhage into the bile ducts, usually from severe liver injury, that produced hæmatemesis and melæna. The first case of traumatic hæmobilia was described one hundred years earlier (Owen, 1848). This was a 22-year-old man who injured his abdomen when thrown from a carriage during a race. He became jaundiced on the third day and on the fifth passed a large amount of blood in the stool and continued to have melæna until his death eleven days after injury. At autopsy, he was found to have had a large laceration of the right lobe of the liver sealed off by the dome of the diaphragm so that there was no free blood in the peritoneal cavity. There was no specific mention of blood in the biliary tract at post-mortem, nor mention of a lesion of the alimentary tract to account for the bleeding. 21 cases of traumatic hæmobilia in all have been reported, 16 of these have had severe hæmatemesis and melæna with a mortality of 50% (Sworn, 1959).

Hæmobilia may result from a variety of causes both inside and outside the liver. Aneurysm of the hepatic artery and its branches accounts for the majority of the cases reported in the literature; by 1954, 96 cases were described, 4 being cured by operation (Quattlebaum, 1954). Tumours of the biliary tract either benign or malignant, ulceration of submucosal vessels by gall stones (Die Blutende Gallenblase—Heusser, 1925) or T-tube (Rabinovitch and Rabinovitch, 1954) may account for bleeding from the biliary tract. Rarer causes include aneurysm of the portal vein eroding into the common bile duct (Barzilai and Kleckner, 1956) and hydatid cyst of the liver (Goulston, 1956).

The following case report illustrates the difficulties in diagnosis and management.

CASE REPORT

T. O'D., male, aged 48, a cleaner, was admitted to St. James' Hospital, Balham, on 17.2.58 as an emergency with forty-eight hours' severe sudden epigastric pain and hæmatemesis. He had vomited a small quantity of bright red blood followed by about 4 pints of altered blood. He had suffered for twenty years from periods of indigestion after bouts of heavy drinking.

On examination he was ill and in pain. There was rigidity and spasm of the upper abdomen. A clinical diagnosis of perforated duodenal ulcer with associated bleeding was made and he was operated on soon after admission.

Operation I, 17.2.58.—Right paramedian incision. No perforation. Small bowel contained blood (4-inch segment at mid-point). No source of bleeding found. The liver was noted to be enlarged and smooth.

On 19.2.58 he developed obstructive jaundice (serum bilirubin 9·2 mg%) and had melæna stools. He continued in this state until 27.2.58 when he had a further laparotomy.

Operation II, 27.2.58 (N.C.T.).—Laparotomy

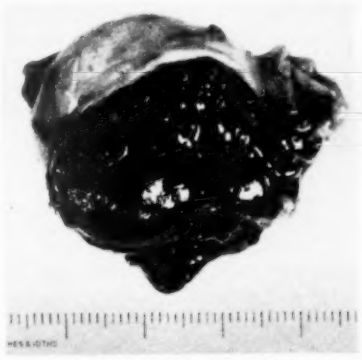


FIG. 1.—Gall bladder tense with clotted blood.

findings: tense gall bladder and common bile duct, yielding black blood and clots on needling. Choledochotomy was performed and thick blood clot removed and a probe was passed down into the duodenum. After removing the clots, clear bile under tension drained through the choledochotomy incision. Cholecystectomy was performed and the common duct drained by Kehr's T-tube (Fig. 1). A choledochogram showed no abnormality in the biliary tree.

Post-operatively, he continued with intermittent jaundice, hæmatemeses, melæna and swinging temperature until:

Operation III, 1.5.58.—Laparotomy. There was generalized enlargement of the liver, the lateral and posterior parts of the right lobe appeared to contain hard, irregular masses—"it looks like a carbuncle" (N.C.T.). No pus was aspirated by multiple needling. The affected part of the liver was removed (right hemihepatectomy). The cut surface of the removed part revealed several cavities and diffuse cholangitis (Fig. 2).

FIG. 2.—Cut surface of the right hemihepatectomy specimen showing irregular cavities and diffuse fibrosis.

The bile ducts were explored and washed out but no abnormality was found. A gauze pack was brought out through the wound.

Histology (Dr. Geoffrey Allen).—"Sections show multiple abscesses mostly in association with bile ducts; periductal fibrosis is extensive and in these areas, irregular duct-like structures are scattered. Recent and old hæmorrhage is frequently seen, the hæmorrhage is considerable. There is no evidence of polyarteritis nodosa."

After this third operation he had further attacks of epigastric pain and three weeks later he began to pass melæna stools, and blood clots from the drainage site in his wound. He was given repeated blood transfusions and continued to have epigastric pain, hæmatemesis and melæna until his fourth and last operation.

Operation IV, 7.8.58.—The cavity left by the previous excision of the right lobe of the liver was filled by a chronic abscess lined with dirty granulations. These were curetted. The common bile duct was very dilated and was again explored and numerous old blood clots and some fresh blood evacuated. Both hepatic ducts were exposed and explored by tube. The left duct was normal and drained clear bile. The right duct was dilated and contained many blood clots. Both ducts were washed out and a T-tube placed in the common duct with its long upper limb passing upwards into the left hepatic duct. The right hepatic duct was ligated at its junction with the left and was transected just proximal to this. A large drainage tube was then passed into the stump of the right hepatic duct and stitched in place. He made good post-operative progress but had one small hæmorrhage from the tube in the right hepatic duct on the twelfth post-operative day; this stopped spontaneously and the tubes were removed. He was discharged home on 4.10.58 and has remained well since. The Wassermann reaction was negative.

The symptoms associated with hæmobilia may include indigestion, flatulence, jaundice, vomiting, upper abdominal and back pain simulating biliary colic or perforation. When the cause is an aneurysm of the hepatic artery, massive alimentary bleeding may occur. The diagnosis of hæmobilia is rarely made before operation and in reported cases was usually made on the third to fifth operation (Mackay and Page, 1959). At laparotomy, if no apparent cause for hæmatemesis is found, the biliary system should be explored for the presence of blood. If blood is found, a cholangiogram should be taken to exclude a lesion in the duct such as a tumour and if this X-ray is normal a hepatic arteriogram should be done to demonstrate the arterial tree. These procedures were carried out by Mackay and Page (1959) to diagnose an aneurysm of the right hepatic artery within the substance of the right lobe of the liver. Their patient was diagnosed at the fourth operation and treated successfully by ligation of the right hepatic artery. Dwight and Ratcliffe (1952) reported 4 cases successfully operated on for hepatic artery aneurysm; 3 were treated by ligation of the common hepatic artery and the other by wiring the aneurysm.

Markowitz *et al.* (1949) showed that after ligation of the hepatic artery in animals, a heavy antibiotic cover prevents liver necrosis. In 1943, Sir Gordon Gordon-Taylor described a woman of 61 with hæmobilia from an aneurysm of the hepatic artery which communicated with the gall bladder. The gall bladder was removed and the breach in the artery closed but the patient died four hours after operation. Resection of the aneurysm and reconstruction of the hepatic artery by end-to-end anastomosis or grafting has been suggested as a possibility with extrahepatic

aneurysm. With an intrahepatic aneurysm, either ligation of the hepatic artery or partial hepatectomy can be considered. Our patient probably had an intrahepatic aneurysm causing the massive repeated bleeding. He needed 74 pints of transfused blood before the bleeding was controlled by hemihepatectomy and ligation of the right hepatic duct.

REFERENCES

BARZILAI, R., and KLECKNER, M. S. (1956) *Arch. Surg., Chicago*, **72,** 725.
DWIGHT, R. W., and RATCLIFFE, J. W. (1952) *Surgery*, **31,** 915.
GORDON-TAYLOR, G. (1943) *Brit. med. J.*, i, 504.
GOULSTON, E. (1956) *Aust. N.Z.J. Surg.*, **25,** 302
HEUSSER, H. (1925) *Münch. med. Wschr.*, **72,** 2007.
MACKAY, A. G., and PAGE, H. G. (1959) *New Engl. J. Med.*, **260,** 468.
MARKOWITZ, J., RAPPAPORT, A., and SCOTT, A. C. (1949) *Proc. Soc. exp. Biol., N.Y.*, **70,** 305.
OWEN, H. K. (1848) *Lond. med. Gaz.*, **7,** 1048.
QUATTLEBAUM, J. K. (1954) *Ann. Surg.*, **139,** 743.
RABINOVITCH, J., and RABINOVITCH, P. (1954) *Arch. Surg., Chicago*, **69,** 849.
SANDBLOM, P. (1948) *Surgery*, **24,** 571.
SWORN, B. R. (1959) *Brit. J. Surg.*, **203,** 254.

Cerebral Abscess Presenting as Larceny.—A. D. M. SMITH, M.B.

R. P. was a normal, well-behaved healthy boy until October 1958 when at the age of 12 he suffered from fever and frontal headaches for a few days. Three months later he started getting into trouble at school because he was belligerent with the other boys and rude and aggressive towards the schoolmistresses. He soon began to steal anything he could easily lay hands on and six months later came before a juvenile court on eight charges of larceny.

The Court placed him in the care of the County Council in June 1959. A month after going to the Reception Centre he developed fever and headache and was kept in bed with a diagnosis of sinusitis. He was recorded as being a very difficult patient who expected to be waited on hand and foot. . . . At the end of July he was admitted to hospital for investigation, but discharged after four days. Except for a swinging temperature up to 102° F in the evenings and a sedimentation rate of 40 mm in the first hour (Wintrobe), no organic trouble was found.

In August 1959, after two months' intractable behaviour in the County Council Home, he was admitted as an emergency to the Central Middlesex Hospital.

Findings on admission.—He was mentally confused and emotionally wildly unstable, his moods fluctuating from surly stupor to maniacal viciousness. He had a swinging fever up to 102° F. Both fundi showed gross papilloedema with hæmorrhages and exudates. He continually shouted, hurling aggressive insults at the staff, and kicking and biting anyone who attempted an injection of any kind. During a violent bout of shouting on the day after admission he lapsed into stupor from the resulting increase in intracranial pressure but recovered after intravenous sucrose.

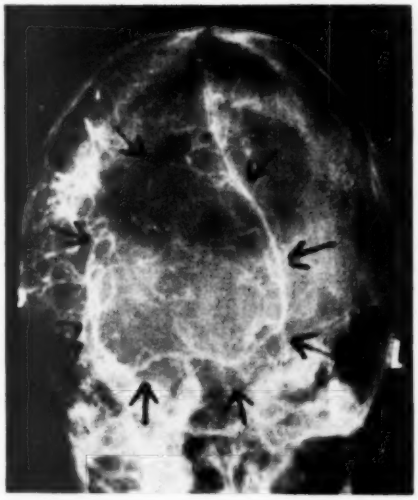


FIG. 1.—Cerebral arteriogram. The site and size of the abscess (*see* arrows) is clearly shown by the displaced vessels.

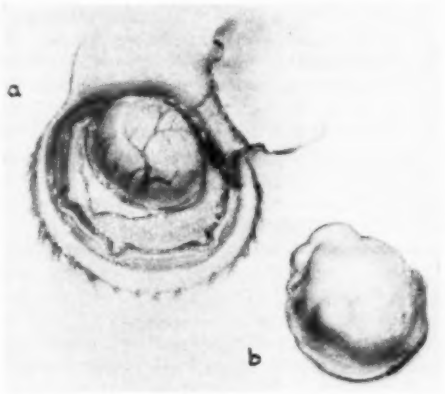


FIG. 2.—A, The abscess as it appeared after the dura was incised. B, The specimen after removal.

He showed no focal neurological signs, but an urgent arteriogram (Fig. 1) showed a massive space-occupying lesion in the right frontal region. W.B.C. 10,000 (normal differential).

Craniotomy, 20.8.59 (Mr. T. G. Illtyd James).—On exploring the right frontal region a firm

rounded mass could be felt. A greyish-yellow sphere, 7·5 cm in diameter, was enucleated and found to be a chronic encapsulated abscess (Fig. 2). The surrounding tissues contained many small satellite dumb-bell abscesses which probably had produced many of his later symptoms. The pus from the abscess grew a β hæmolytic streptococcus.

Post-operative course.—Penicillin and sulphadimidine were given for the next two weeks. He progressed uneventfully apart from loss of body-image for the first six days after operation; this symptom resolved completely overnight.

Psychological course.—Soon after the operation he emerged as a friendly, likeable little boy whose behaviour was perfectly normal. The only effect of his illness was that he was somewhat undersized for his age. He remains physically and mentally normal six months later and there has been no return of his psychopathic behaviour.

Comment.—This case is interesting because the first symptom was petty thieving—a crime which brought him under the State's jurisdiction as a delinquent child.

Acknowledgments.—My thanks are due to Miss Barber, medical artist, for the drawing and Dr. F. Pygott for the arteriogram.

Investigation and Treatment of Unusual Symptoms after Partial Gastrectomy.—J. E. LENNARD-JONES, M.B., M.R.C.P.[1] (for E. N. ROWLANDS, M.D., F.R.C.P.).

The severe symptoms which this patient experienced after partial gastrectomy appeared to be largely neurotic but experimental investigation demonstrated their reality and their cause.

Background history.—When aged 41, Miss D. W. began to suffer periodic bouts of epigastric pain after meals. The pain was often severe enough to make her sweat and force her to lie down; it kept her away from work for several months each year. A benign ulcer was repeatedly observed high on the lesser curve of the stomach. For seven years she was treated medically, but during that time she had four hæmatemeses and her bouts of pain became more frequent and more severe. The need for surgery became obvious and a Polya-type partial gastrectomy was performed.

After the operation she rapidly lost weight and was very miserable because of copious bilious vomiting. Barium meals showed that all the barium entered the dilated afferent loop of the gastrectomy, and none the efferent loop; therefore an entero-enterostomy was constructed. After this, barium passed satisfactorily through the anastomosis from the afferent to the efferent loop but she was no better. After three months a Roux-en-Y reconstruction was performed at a third operation.

For the following six years she has remained an invalid on account of pain. She has been free of bilious vomiting, but tends to vomit food if she stoops after a meal. Her weight has remained low (to maintain it, she gives herself a gastric drip of milk every night) and she passes frequent bulky offensive stools.

Her present pain (*Fig.* 1).—As soon as she eats

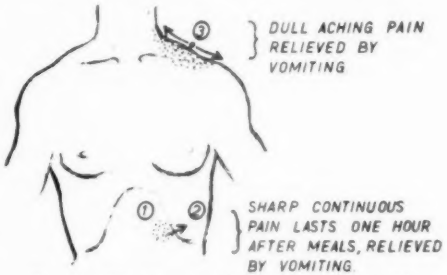


FIG. 1.—The sites of pain (*see* text for details).

or drinks, a sharp continuous pain develops just below the left costal margin at the level of the ninth rib (1). As she continues eating this pain spreads laterally (2) for about 15 cm, becoming more severe as more food is eaten. The pain persists for about an hour after a meal and then gradually disappears; it can be relieved completely by self-induced vomiting and slightly relieved by lying down or taking alkalis. If she continues eating a dull aching pain develops behind the crest of the left shoulder (3) and spreads upwards behind the left ear and outwards over the acromion.

Routine investigations.—(1) *General:* Hb and blood levels of Na, K, Ca, PO_4 and alkaline phosphatase normal. No occult blood detected in stools. Fæcal fat excretion 13 g daily (80 g fat diet), reduced to 10 g by giving 8 g of pancreatin daily.

(2) *X-ray studies:* The stomach remnant is pouch-like with a single stoma, high, anteriorly and to the left (Fig. 2). Continuous, vigorous and irregular contractions of the pouch squirt small quantities of barium through the stoma every few seconds; 150 ml of thin barium takes one to two hours to pass into the jejunum.

(3) *Acid secretion:* An "augmented histamine" test yielded 3 ml of fluid with a pH of 4·5. (Acid loss from the gastric remnant was unlikely due to the anatomical arrangement.) The contents of the pouch were aspirated every hour for twenty-four hours but yielded no sample with a pH more acid than 4·5. No urinary pepsinogen was detectable. These investigations conclusively demonstrate achlorhydria.

[1]Member Scientific Staff, Medical Research Council.

FIG. 2.—The gastric pouch after the Roux-en-Y reconstruction.

Investigation of her pain.—(1) *Factors exonerated:* X-rays do not reveal a stomal ulcer, which is not surprising as the stomach remnant produces no acid. The pain is brought on by drinking only 10 ml of fluid, and is not relieved when the patient lies flat or with her head below the level of her feet, so gravitational pull on the supports of the gastric pouch is therefore an unlikely cause. Furthermore, upward pull on the tube of a fluid-filled balloon in the pouch, supporting the weight of the balloon, does not relieve the pain. Bread soaked in barium produces pain when it enters the gastric pouch and before it enters the jejunum, and conversely, fluid infused through a tube directly into the jejunum causes no pain, excluding pain due to jejunal distension. A purely psychological explanation for the pain is untenable since fluid apparently infused through a tube into the stomach remnant, but actually infused into the jejunum or diverted down a side-arm, without the patient's knowledge, does not produce pain.

(2) *Factors incriminated:* The writhing contractions which begin as soon as any food enters the gastric remnant appear to be responsible for pain since the contractions stop and the pain is immediately relieved when hyoscine n-butylobromide, 10 mg (Buscopan), is given intravenously; saline given in the same way has no effect. The pain is completely relieved in this way only when the gastric pouch contains less than 60 ml of fluid. Distension of the pouch by inflating a balloon in it causes pain. Small volumes (up to 60 ml) of fluid in the balloon cause localized epigastric pain (Fig. 1) which can be relieved by Buscopan; if, after giving Buscopan, another 100–200 ml of fluid is introduced the pain reappears and spreads laterally. When 200 ml is reached the pain begins in the crest of the left shoulder and radiates upwards and outwards as more fluid is added. The pain in the shoulder is not due to distension of the cardia for inflation of a balloon there produces a retrosternal "bursting" pain unfamiliar to the patient.

Medical treatment.—All the abdominal and thoracic pain can be relieved both experimentally and clinically by giving 30 ml of 2% lignocaine in carboxymethyl cellulose (Xylocaine Viscous). The pain in the crest of the shoulder is not relieved by this drug, suggesting that it arises outside the stomach wall. For over a year, while she has taken Xylocaine Viscous 30 ml q.d.s. before meals, our patient has been free of abdominal pain.

Comment.—Local anæsthetics have been used previously in the treatment of post-gastrectomy symptoms (Meurling, 1948; Dardel and Morales, 1951). We have used slightly more than the maximum safe oral dose of lignocaine suggested by animal experiments (Wiedling, 1952). No toxic effects from prolonged oral administration of lignocaine have so far been reported.

The patient still tends to vomit if she stoops after a meal, still has to take small meals, and her weight remains low. It is possible that further surgical treatment should be undertaken now that the mechanism of her symptoms is better understood, but she is understandably reluctant to undergo another operation.

REFERENCES

DARDEL, O. VON, and MORALES, O. (1951) *Nord. med.*, **45**, 469.
MEURLING, S. (1948) *Nord. med.*, **39**, 1533.
WIEDLING, S. (1952) *Acta pharm. tox., Kbh.*, **8**, 117.

The following cases were also shown:

Essential Cryoglobulinæmia.—DR. R. J. HARRISON, DR. A. S. MCFARLANE and DR. A. BRUCE-ROBERTSON.

Islet Cell Tumour of the Pancreas Presenting as Hysteria.—MR. R. M. KIRK (for MR. N. TANNER).

Islet Cell Tumour Presenting as Hysteria.—DR. RICHARD ASHER (*see Proceedings*, 1960, **53**, 217).

Malabsorption Syndrome with Pancreatic Calcification and Jejunal Diverticulosis.—DR. R. L. HEWER (for DR. H. WYKEHAM BALME).

Bilateral Chylothorax due to Follicular Lymphoma.—DR. W. B. THOMSON (for DR. R. D. GREEN).

Meeting
December 11, 1959

An Unusual Case of Meckel's Diverticulum.—PAUL T. SAVAGE, F.R.C.S.

History.—A man, aged 29, first complained of lack of energy and attacks of colicky abdominal pain two years ago. After six months he attended another hospital where he was found to be anæmic (Hb 63%). A barium meal showed no abnormality of his stomach or duodenum. His anæmia was ascribed to dietary deficiency; iron given by mouth did not raise his hæmoglobin but after a course of Ferrivenin (500 mg) his hæmoglobin rose to 70%.

Five months ago he again complained of colicky abdominal pain, mostly at night, and progressive loss of energy, weakness and breathlessness on exertion. He noticed that his stools were black (at the time he was not taking iron by mouth).

Physical examination.—Very pale and thin. Bilateral coloboma of iris. No other abnormal physical signs.

Investigations.—Hæmoglobin on admission 31%. The anæmia was of the iron-deficiency type. Examination of stools for occult blood was positive on three separate occasions. A barium meal showed no abnormality of stomach or duodenum but the follow-through suggested there was malrotation of the gut, with the duodeno-jejunal flexure on the right and the cæcum over on the left. A piriform diverticulum 4 × 3 in. (10 × 7·5 cm) was well shown, filling from the ileum. It lay in the left hypochondrium, its fundus reaching almost as high as the left dome of the diaphragm (Fig. 1).

Progress and treatment.—Imferon, 5 c.c daily for twenty-two days, raised his hæmoglobin to 76%.

Laparotomy (P. T. S.).—15.5.59: The abdomen was opened through a 6-inch (15 cm) upper mid-line incision. The duodenum was found to pass behind the superior mesenteric vessels in the usual way and the duodeno-jejunal flexure lay in its proper place, behind the left side of the root of the transverse mesocolon. The terminal ileum, cæcum, ascending colon, hepatic flexure and transverse colon all lay on a common mesentery, which in the region of the cæcum was about 14 in. (35 cm) long. A large Meckel's diverticulum 4 × 3 in. (10 × 7·5 cm) was found 16 in. (41 cm) proximal to the ileocæcal valve. The terminal ileum, Meckel's diverticulum, cæcum and ascending colon were twisted through three complete turns, forming an ileocæcal volvulus (Fig. 2). On untwisting the volvulus, the long common ileocolic mesentery was seen to be narrowed between the ascending colon and the ileum at the level of the Meckel's diverticulum, to only 3 in. (7·5 cm) in width

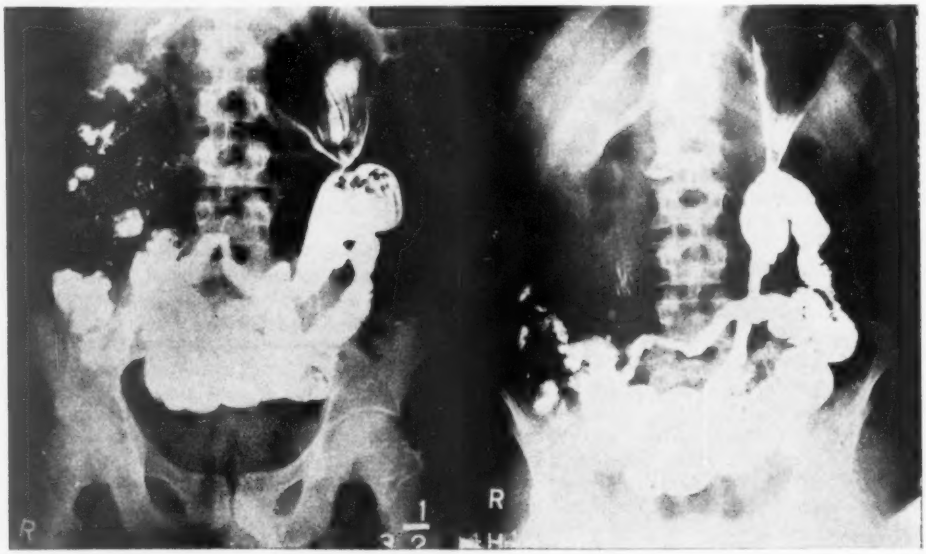


FIG. 1.—Barium follow-through at three and a half and four hours showing a large Meckel's diverticulum filled partly with air and partly with barium.

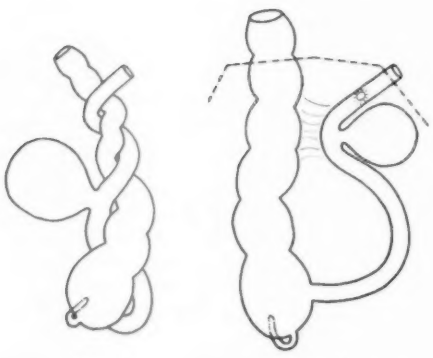


FIG. 2. FIG. 3.

FIG. 2.—Ileocæcal volvulus involving Meckel's diverticulum.

FIG. 3.—There is narrowing of the common mesentery between the ileum and the ascending colon, at the site of the Meckel's diverticulum. A superficial ileal ulcer ¾ in. in diameter was found 2 in. proximal to the Meckel's diverticulum.

(Fig. 3). An ileocolic resection was carried out, the terminal ileum, Meckel's diverticulum, cæcum and ascending colon being excised, and continuity of the bowel restored by end-to-end anastomosis. Convalescence was uneventful.

Examination of the specimen showed a superficial ulcer ¾ in. (2 cm) in diameter in the ileum, 2 in. (5 cm) proximal to the Meckel's diverticulum. Neither the Meckel's diverticulum nor the adjacent ileum contained any gastric mucosa and the pathogenesis of this ulcer remains a mystery.

Follow-up.—The patient has remained well and free from colic and anæmia since his operation.

Subacute Bacterial Infection in a Traumatic Arteriovenous Fistula.—MARTIN BIRNSTINGL, M.S., F.R.C.S.

Male, aged 38. Orthopædic technician.

Clinical history.—June 1959: Gradual onset of lassitude and exhaustion. During next three months lost 2½ st. weight. October 1959: Fever with rigors. Treated with oral penicillin and sulphonamides, but symptoms returned on cessation.

Admitted to Chase Farm Hospital, Enfield (Dr. C. Allan Birch). During investigation of pyrexia found to have a positive blood culture (*Str. viridans*) and a symptomless traumatic arteriovenous fistula of left thigh which was assumed to be the nidus of the infection.

After three weeks' penicillin treatment he was transferred to the Surgical Unit, St. Bartholomew's Hospital.

Past history.—1943: In N. Africa, he received multiple gun-shot wounds, losing his left eye. A few weeks later he noticed a buzzing sensation in his left thigh but the fistula was not detected when he was discharged from the Army. 1944: Infective hepatitis.

On examination 28.10.59.—Mild intermittent fever to 100·4° F. No clubbing of fingers. No embolic lesions seen.

Heart: Cardiac impulse forceful. No left ventricular hypertrophy. Heart sounds normal. Grade II ejection systolic murmur. No diastolic murmur. Brachial blood pressure 120/60. Radial pulse collapsing.

Abdomen: Spleen enlarged 3 fingerbreadths below ribs.

Left lower limb: Skin, colour and nutrition normal. No enlarged veins. Left femoral pulsation greatly increased. Distal leg pulses present. Marked thrill felt over femoral vessels in middle third of thigh. Loud, continuous murmur on auscultation.

Branham's test.—Pulse-rate before femoral compression 76, after femoral compression 68/minute.

Investigations.—Hæmoglobin 11·4 g/100 ml. W.B.C. 6,000, normal differential. E.S.R. 35 mm in first hour (Westergren). Blood cultures (28.10.59, 29.10.59, 30.10.59): Growth of *Str. viridans* (organism inhibited by 0·06 unit penicillin per ml; standard staphylococcus inhibited by 0·03 unit per ml).

Urine: Centrifuged deposit. Small numbers of red blood cells. Occasional leucocytes. Culture sterile.

Chest X-ray: Heart size 13 cm. No evidence of enlargement. Heart screening normal. ECG normal.

Femoral arteriography (Fig. 1).—Large fistula between femoral artery and femoral vein in middle third of thigh. Artery proximal to the fistula appears greatly widened. Distal arteries appear normal.

Treatment.—1.11.59: Soluble penicillin 1·5 mega units I.M. six-hourly.

Operation (4.12.59).—Closure of arteriovenous fistula (Mr. G. W. Taylor). The femoral artery communicated with the vein by a short sac, forming a channel 1 cm long and 0·7 cm in diameter at its narrowest point. Small vegetations present within sac and on femoral vein close to the fistula (Fig. 2).

Sac excised and resulting defects in artery and vein sutured longitudinally to restore continuity of both. Bacterial examination of the vegetations was omitted, but Gram-positive cocci were visible in stained histological sections.

Progress.—Penicillin continued for four weeks following operation. Six weeks later he was

FIG. 1.—Percutaneous femoral arteriogram (Dr. J. K. Davidson) showing large communication with femoral vein. There is marked dilatation of the femoral artery above the fistula.

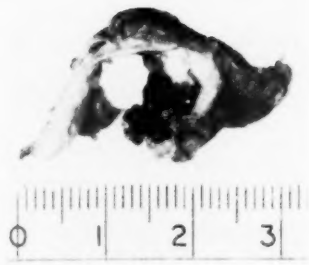


FIG. 2.—Photograph of excised sac of arteriovenous fistula. There is a small mass of dark vegetations below and to the right of the orifice, which is seen from the venous aspect (scale in cm).

symptom free and the distal pulses in the leg were still easily palpable.

Comment.—Bacterial infection is a rare complication of traumatic arteriovenous fistula and the first surgical cure was reported by Hamman and Rienhoff (1935). The large fistula in this man was similar to those reported, most of which had been established for several years. Bacterial endocarditis co-existed with the endarteritis in 9 of the 23 cases recorded in the literature (Parmley *et al.*, 1954; Curtin *et al.*, 1957; Hook *et al.*, 1957) but was not found in this case. Infection is not uncommon in experimental arteriovenous shunts in animals (Lillehei *et al.*, 1953).

The pre-operative arteriograms clearly demonstrate the fistula and show gross proximal dilatation of the femoral artery above the shunt (Fig. 1). Evidence has been provided by Holman (1937) that this phenomenon is the result of the great increase in blood flow through the artery towards the fistula.

The closure of the defect, which was about the diameter of a pencil (Fig. 2), raised no special problem and it was possible to repair the openings in both the artery and vein, without impairing the final flow along either.

Acknowledgment.—I am indebted to Dr. C. Allan Birch and Mr. G. W. Taylor for permission to publish this case.

REFERENCES

CURTIN, J. A., PETERSDORF, R. G., and BENNETT, I. L. (1957) *Bull. Johns Hopk. Hosp.*, **101**, 140.
HAMMAN, L., and RIENHOFF, W. F. (1935) *Bull. Johns Hopk. Hosp.*, **57**, 219.
HOLMAN, E. (1937) Arteriovenous Aneurysm. New York.
HOOK, E. W., WAINER, H. S., MCGEE, T. J., and SELLERS, T. F. (1957) *J. Amer. med. Ass.*, **164**, 1450.
LILLEHEI, C. W., WARGO, J. D., and HAMMERSTROM, R. N. (1953) *Dis. Chest*, **24**, 421.
PARMLEY, L. F., ORBISON, J. A., HUGHES, C. W., and MATTINGLY, T. W. (1954) *New Engl. J. med.*, **250**, 305.

The following cases were also shown:

Pilonidal Sinus: Demonstration of Hair Entry.—Mr. B. H. PAGE.

(1) Subpleural Lipoma Causing Rib Erosion. (2) Renal or Adrenal Cyst.—Miss MURIEL C. WATERFALL.

Palliative Operation for Ascites in Cirrhosis Hepatis.—Mr. PETER KNIPE (*see* GIRLING, J. A. (1959) *Proc. R. Soc. Med.*, **52**, 252). Since her discharge from hospital over a year ago the serum albumin has steadily risen and has been accompanied by improving health. She has had no further ascites or œdema.

Innominate Vein Thrombosis and Sarcoidosis.—Dr. P. H. N. WOOD.

Mesenteric Venous Thrombosis in a Patient with Thrombocytopenia.—Mr. W. M. KEYNES.

Sculptured grace . . . and a special

kind of motoring which no other car

in the world can offer

JAGUAR

One of the Trophies won by Jaguar in their Le Mans victories of 1951, 1953, 1955, 1956, 1957

LONDON SHOWROOMS · 88 PICCADILLY · W.1

A selection of new titles from Pergamon Press

INHIBITION IN THE NERVOUS SYSTEM AND γ-AMINOBUTYRIC ACID

Edited by EUGENE ROBERTS

Proceedings of a symposium held at Duarte, California, sponsored by the U.S. Air Force Office of Scientific Research.

Approx. £7 net ($20.00)

PHYSIOLOGICAL MECHANISMS CONCERNED WITH CONCEPTION

Proceedings of a conference sponsored by The Population Council and Planned Parenthood Federation of America, held in New York.

In preparation

PSYCHOLOGY, COLLECTA OF SOVIET WORK

Edited by N. O'CONNOR

Collection of Russian work in psychology from 1917 to date, together with a complete bibliography.

In preparation

CHEMICAL PATHOLOGY OF THE NERVOUS SYSTEM

Edited by J. FOLCH-PI

Proceedings of the Third International Neurological Symposium, Strasbourg.

In preparation

CHOLINESTERASES

By M. A. GEREBTZOFF

The histochemical research forming the basis of this book represents six years of team work in the Department of Anatomy Laboratory, Liège University.

55s. net ($8.50)

CONCEPTS OF MEDICINE

Edited by BRANDON LUSH

This book aims to make members of the medical profession, especially the younger ones, think more widely about medicine—its present stage of development, its trends for the future, its place in society, its place as university discipline, as a vocation, etc.

Approx. 40s. net ($6.00)

PHOSPHORUS METABOLISM OF BRAIN

By P. J. HEALD

Assessment of work relating to the metabolism of phosphate derivates in the central nervous system as affected by changes in the functional activity of the brain.

In preparation

PHYSIOLOGY IN INDUSTRY

By LUCIEN BROUHA

The first marriage of physiology and industrial engineering to produce a new scientific approach in human engineering.

40s. net ($6.50)

Please write for fully descriptive leaflets

PERGAMON PRESS

OXFORD : LONDON : NEW YORK : PARIS

Headington Hill Hall, Oxford — 4 & 5 Fitzroy Square, London, W.1

122 East 55th Street, New York 22, N.Y. — 24 Rue des Écoles, Paris Ve

BOOK REVIEWS

Medical Discoveries: Who and When. By J. E. Schmidt, Ph.B.S., M.D., Litt.D. (Pp. 555. £5 18s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

In this book some 6,000 medical and related scientific discoveries are listed in alphabetical order under what are considered to be appropriate catchwords or headings. The subjects covered include diseases, anatomical structures, operations, instruments, tests, methods, syndromes and theories, and the work is designed to provide a rapid answer to such questions as "When and by whom were rubber gloves introduced in surgery? Who first described osteomalacia? When was sodium citrate first recognized as an anticoagulant? When was the clinical thermometer introduced?" The basic information given in each entry consists of name of discoverer or inventor, nationality, profession, dates of birth and death, and date of the discovery or contribution.

Despite what is said in the preface, it is very difficult to justify some of the headings used in the dictionary and there is much overlapping. Thus Esdaile's work is entered under "Anesthesia, hypnotic, early induction of," but Elliotson's is under "Surgical operations with aid of hypnotism". There are entries under "Insane, abandonment of chains and fetters for" and under "No-restraint method of treating insane". Apart from the question of duplication many of these cumbersome headings could profitably be reduced to one or two words.

Proper evaluation of any work of this kind can only be made after a long period of regular use, but at first sight the coverage appears to be remarkably complete and the information accurate. It is obvious that the compiler owes a heavy debt to Dobson, Emerson, Kelly, Fischer, Garrison, Morton, Skinner and others, but no acknowledgment is made to earlier workers in this complex and difficult field.

Rheumatic Fever: Epidemiology and Prevention. The Proceedings of a Seminar held at the International Children's Centre, Paris, September 25–27, 1956. Editors: R. Cruickshank, M.D., Ch.B., F.R.C.P., D.P.H., and A. A. Glynn, M.B., B.S., M.R.C.P. (Pp. 193; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1959.

This book reports the contributions to a Seminar held in Paris in 1956. The original French edition was prepared by Dr. Raymond Gautier, and the English edition was delayed by his sudden death in 1957.

As would be expected, this is really a book about the Group A hæmolytic streptococcus, and the first two sections of the book are devoted to the biological and epidemiological aspects of this sinister organism. The third section presents and weighs up the evidence for the relationship between streptococcal infections and rheumatic fever, but four papers are also included which suggest that other factors may also be important. Thus Bywaters seeks to answer the more complex problem of why such infections are only followed by rheumatic fever in an extremely small and selected number of the population, admitting inheritance and secretor status as perhaps determining undue susceptibility.

The final section of the book deals with the prevention of rheumatic fever, and is the practical product of, and justification for, the three preceding sections. There is a great deal of information in the book, and although the papers are all excellent in themselves, they do not advance our knowledge a great deal.

A Primer of Water, Electrolyte and Acid-Base Syndromes. By Emanuel Goldberger, M.D., F.A.C.P. (Pp. 322; illustrated. 45s.) London: Henry Kimpton. 1959.

This book begins with a discussion of the distribution of the body fluids and electrolytes, followed by a description of the various disturbances of body fluid balance and the manner in which they should be managed. In the second half of the book problems of acid-base balance are similarly dealt with. Throughout, the problems are discussed from an essentially physico-chemical standpoint, and there are useful explanations of some of the basic concepts of this nature involved in body fluid balance. At the same time this approach results in an unduly complex academic, laboratory view of many of the problems. Thus, in discussing the treatment of sodium deficits, three methods are described of calculating the amount of replacement fluid required, based respectively on the patient's body-weight, on hæmatocrit and on serum sodium concentration, but no mention is made of the importance of assessing clinically the patient's response to treatment.

In a relatively short text this book covers most aspects of the broad problem of disturbances of body fluid equilibrium. But many practising clinicians, for whom this primer is intended, may

well find its mass of detailed information confusing, and its value is undoubtedly curtailed by insufficient emphasis on the important facts and principles of the subject.

Acute Cardiac Pulmonary Edema. By Sigmund Wassermann, M.D. (Pp. x+123. 34s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

A number of the author's friends and admirers have added their names to this small book, wishing to pay tribute to a profound reader, keen observer and research worker, superb clinician and humanist.

The text takes the form of an essay on cardiac pulmonary œdema where the attack is described and the history and clinical findings in several patients exhibiting the syndrome are cited. The work of other authors is fully acknowledged and the theories they have put forward often accepted and sometimes rejected.

The condition is defined as a reflex syndrome involving the cardiopulmonary segments of the autonomic nervous system, and a confirmation of this view is assumed from the suppression of an attack on occasion from carotid sinus or ocular pressure. The thesis of a decreasing load on the left ventricle and pulmonary stasis is rejected as an explanation of the improvement caused by such manœuvres.

The only criticism that can be justly aimed at this book, with its commendable purpose, is that although cardiac asthma is said to differ from acute cardiac pulmonary œdema, the differentiation between the two conditions has not been clearly made, presumably because this is not always possible, or is at least often difficult.

Medical X-ray Technique. Principles and Practice. By G. J. van der Plaats. Translated by G. E. Luton. (Pp. xii+480; illustrated. 57s. 6d.) Eindhoven: Philips' Technical Library. 1959.

This book does not in the main describe positions of the patient for carrying out the various X-ray examinations, but deals comprehensively with most other technical aspects of radiography.

The author gives an account of the nature of X-rays and of the design and construction of X-ray tubes. He then discusses the properties of X-rays and indicates, on a fairly elementary plane, the physical principles underlying the formation of the X-ray image and the laws of projection. Some chapters are devoted to the various qualities of an X-ray image with a detailed description of those factors which determine the sharpness and contrast of the image.

The book then deals with accessories such as intensifying screens, grids, &c., and their function, and with the processing of the film. Of special value is a discussion of the influence of kilovoltage on the radiographic image with a particular emphasis on using a high kilovoltage wherever possible.

The author describes special radiographic techniques such as tomography and bronchography but the value of the volume lies less in these than in the other sections. Eight chapters are devoted to the physical and technical aspects of radiation therapy.

For the student of radiography this book very adequately covers the technical field. For the radiology student it is an excellent and readable introduction although rather elementary on the physics side. A minor criticism is that in places some of the illustrations are rather far removed from the relevant text. Within its limits, this book does its job admirably and can be recommended.

Chemical and Molecular Basis of Nerve Activity. By David Nachmansohn. (Pp. xi–235; illustrated. $7.50.) New York: Academic Press, Inc. 1959.

This book, whose author has won distinction in the field to which it is devoted, covers most of the important aspects of nerve activity from the chemical point of view. It commences with an account of the physical events which accompany nerve activity and then introduces the reader to the neurohumoral transmission theory. This is followed by longer chapters on acetylcholinesterase, the action of its inhibitors and the sequence of energy transformations. In these chapters the author's own contributions, stemming from Meyerhof's pioneer studies in enzyme chemistry, are given the prominence they deserve. A short statement on the role of the acetylcholine system introduces further chapters on the mechanism of reactions catalysed by acetylcholinesterase, on nerve gases, insecticides and their antidotes, and the action of acetylcholine on the receptor in intact cells. A chapter is devoted to the effects of lipid soluble quaternary ammonium compounds on conduction. After a brief discussion of the complex and obscure factors determining the changes in permeability of the axon which accompany transmission of the nerve impulse, the book concludes with chapters on transmission at synapses, including the end plates, whose ultrastructure as revealed by electron microscopy is taken into account. The book is very clearly written and should be carefully studied not only by physiologists and pharmacologists but also by those treating patients with diseases of the nervous system.

Butterworths

GENERAL ANAESTHESIA

Edited by FRANKIS T. EVANS, M.B., B.S., F.F.A.R.C.S., D.A., and CECIL GRAY, M.D., F.F.A.R.C.S., D.A. In two volumes: Vol. I: Pp. xiv + 531 + Index. Vol. II: Pp. xii + 431 + Index. 199 illustrations. £7 7s. net, per set, by post 2s. 9d. extra.

The whole wide field of anaesthesia is covered in these two volumes. The first takes in basic principles, covering those specialized aspects of anatomy, physiology and neurophysiology which are important to anaesthetists in their everyday work, pre-anaesthetic considerations, apparatus, blood transfusions, the different methods of administration and many other subjects. Techniques, special fields and hazards are detailed in the second, where the appropriate anaesthetic approach to every type of operation is minutely examined by accepted authorities writing on their own subjects.

HANDBOOK OF HAEMATOLOGICAL AND BLOOD TRANSFUSION TECHNIQUE

By J. W. DELANEY, F.I.M.L.T. Pp. xii + 293 + Index. 50 illustrations. 4 colour plates. 45s. net, by post 2s. extra.

This book, written primarily for the requirements of the laboratory technician, is a valuable addition to current literature on this subject. The section on haematology ranges from the basic techniques to the elucidation of the aetiology of blood disorders, and that on blood transfusion technique deals with all the laboratory work in this field. Here is everything that is required by those working for the examination of the Institute of Medical Laboratory Technology, and is a useful and comprehensive guide for both study and reference.

THE BORDERLAND of EMBRYOLOGY and PATHOLOGY

By R. A. WILLIS, D.Sc., M.D., F.R.C.P. Pp. xii + 627 + Index. 250 illustrations. 90s. net, by post 2s. 3d. extra.

"There is little doubt that this will become a standard reference work for pathologists and we hope that it will be read as well as referred to. It can be equally warmly recommended to obstetricians and gynaecologists and to paediatricians, all of whom will find it a mine of information and stimulating reading."—*Journal of Obstetrics and Gynaecology of the British Empire.*

Full details of these books and an illustrated catalogue will be sent on request.

Butterworths, 88 · Kingsway · London W·C·2

Showroom: 11-12 Bell Yard, Temple Bar, London, W.C.2

Publication Rules

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors, Royal Society of Medicine . . . the copyright of all papers presented at meetings by Fellows of the Society or Members of the Sections (other than those which have been previously published) shall be deemed to be the property of the Society until a decision has been made by the Society in regard to their publication.

Digests: Requests for permission to make Digests from the *Proceedings* should be addressed to the Honorary Editors, Royal Society of Medicine.

Manuscripts should be concise and *carefully revised for press*. They must be top copies, typewritten in double spacing, with the author's name, degrees and address on the first page. A carbon copy should be retained by the author.

The text must contain references to all tables and illustrations; these should be numbered separately, tables in Roman and illustrations in Arabic numerals.

Dosages and other measurements should be given in metric units.

A key should be supplied for all abbreviations and symbols used in text and pictures.

References: The Harvard system should be followed, i.e. each work should be cited in the text by the author's name and date of publication, and at the end of the paper a list should be given in alphabetical order according to the authors' names. Names of journals should be abbreviated in accordance with the "World List of Scientific Periodicals", e.g.

ATKINSON, J. (1921) J. biol. Chem., 47, 134.

With the title of a book the place of publication should be given.

Illustrations: Only the minimum number of illustrations can be accepted. They must be suitable for direct photographic reproduction; films and slides are not accepted.

Important areas should be *lightly* marked in pencil on the *back* of the picture; the top of each picture should be indicated.

Photographs, radiographs and photomicrographs should be sharp black-and-white glossy prints. Photomicrographs of width 2½ in. can be reproduced actual size; magnification must be stated.

Diagrams and graphs should be drawn in Indian ink, on smooth white paper or board. If graph paper is used it should be feint blue-lined. Lines and curves must be boldly drawn, with lettering and numbers sufficiently large to permit of considerable reduction.

Blocks used for the illustration of articles in the *Proceedings* will be presented to authors shortly after each volume is concluded.

Reprints and excerpts: Authors may obtain these from the Society's printers, Messrs. Staples Printers Limited, 83-91, Great Titchfield Street, London, W.1. The appropriate order form will be sent with proofs of papers.

Others requiring single reprints should apply direct to the author. Alternatively, Sectional fasciculi may be purchased from:

The Honorary Editors,
Royal Society of Medicine,
1 Wimpole Street,
London, W.1

Biochemical Aspects of Neurological Disorders. Edited by John N. Cumings, M.D., F.R.C.P., and Michael Kremer, M.D., B.Sc., F.R.C.P. (Pp. x+230; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Within the past few years there has been an awakening interest in the biochemical and metabolic disorders underlying certain diseases of the nervous system, and this collection of nineteen lectures reflects this new and welcome trend. All are interesting, but some more important than others in that they are richer in new information. Amongst those of outstanding interest are Dr. Spillane's lecture on the vitamin-B group of disorders, Professor Thompson's on the biochemical aspects of enzyme disorders, and Professor Rimington's on the biochemistry of porphyrin disorders.

The clinical papers on the neurolipidoses and on the forms of disorders of muscle are too brief to do justice to their subjects Dr. Kremer gives an admirable summary of current knowledge of neurological disorders in liver disease, and Professor Cumings deals with the biochemical aspects of copper metabolism. Time has caught up upon this article in some respects, for it is doubtful if anyone with recent experience would endorse his statements that ββ-dimethylcysteine hydrochloride (Penicillamine) is a less effective cupruretic than BAL, or less effective in the clinical response it produces in many cases. This response is notably greater than Professor Cumings' final paragraph would lead the reader to suppose, and Penicillamine has now become the standard substance in use for the treatment of Wilson's disease.

This volume should find a place in every neurologist's library.

Cancer. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. (Vol. 6. Pp. ix+500+17; illustrated. 85s.) London: Butterworth & Co. (Publishers) Ltd. 1959.

This volume, the last in the series apart from the general index, consists of Part X on Chemotherapy, which occupies two-thirds of the volume, and Part XI on Public Health and Nursing Aspects of Cancer. The section on chemotherapy is particularly valuable in that it assembles information otherwise not readily available on this new aspect of cancer treatment. After an initial chapter on the experimental background of chemotherapy, three chapters follow on its application to carcinoma and the leukæmias. The remainder of the chemotherapeutic section provides an up-to-date detailed guide to the hormonal treatment of breast and prostatic cancer. Two things impress: the enormous amount of work that has been done to try to elucidate the mode of action of hormonal treatment of cancer and, in spite of this, how little we still know. But anyone seeking information on the present state of our knowledge will find it here.

In Part XI your reviewer noted some wise remarks of Professor Haddow in the final chapter on the role of organization in cancer research: "Key discoveries are by no means always made by the most intellectually gifted, nor do the most fertile ideas come from the hardest worker"; and "not all the organization in the world can engender the pregnant idea".

The Operation of Sterilizing Autoclaves. A Symposium held at Brighton Technical College, School of Pharmacy, May 9, 1959. (Pp. 45. 7s. 6d.) London: The Pharmaceutical Press. 1959.

This report is of interest mainly to those directly concerned with autoclaving or the provision of autoclaving facilities. R. H. Maxwell Savage deals with some of the theoretical aspects and is concerned mainly with the sterilization of surgical dressings. G. R. Wilkinson considers the design of autoclaves, and after a brief historical review of steam sterilization he reviews details of equipment, including vacuum pumps and automatic operation. J. C. Kelsey comes to the conclusion that the most important routine check of autoclaving is the daily inspection of the temperature record; also that Browne's colour indicator tubes give more useful information than other methods such as bacteriological tests and avoid the delay inherent in the latter. J. H. Bowie emphasizes the responsibility of hospital management in providing satisfactory sterilizing services, and gives a most interesting description of a process for rapid cooling of autoclaved bottles of liquids.

The report of the discussion merely serves to emphasize that agreement has not yet been reached on many practical points of operation.

Cutaneous Manifestations of the Malignant Lymphomas. By Samuel M. Bluefarb, B.S., M.D., F.A.C.P. (Pp. xiv+534; illustrated. £6 4s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

The "malignant lymphomas" to which the title of this book refers are mycosis fungoides, Hodgkin's disease, and lymphosarcoma. All aspects of mycosis fungoides are described and discussed very fully and clearly; a list of thirteen synonyms is given and the chapter on the history of the condition is a model of what such a chapter should be. Two unusual views are put forward with good supporting evidence: that the

so-called erythroderma form, "homme rouge", is always "lymphocytic leukemia, Hodgkin's disease, reticulum cell lymphosarcoma or some other form of malignancy, . . . not mycosis fungoides", and that the *tumor d'emblée* type is "lymphosarcoma rather than mycosis fungoides". Unfortunately the section on Hodgkin's disease lacks a list of synonyms and has a negligible historical introduction. Pathogenesis is discussed relatively briefly and there is no mention of the Rose Research carried out so thoroughly at St. Bartholomew's Hospital between the wars. The full account of the cutaneous manifestations is admirable. In the preface it is stated most reasonably that the classification of lymphosarcomata is best left to cytologists and that a detailed study of their various types has not been undertaken because the cutaneous manifestations of the various types are essentially the same. These manifestations are described fully.

The last part of the book is entitled "Immunological Status of the Malignant Lymphomas". In it the scattered work on this aspect of the subject is brought together and set out clearly. Each section ends with an immense and truly international bibliography. It is an unusual pleasure to see the French literature receiving its just deserts.

This is an excellent book and must become the standard work of reference in English on its subject. It is strongly recommended, especially to dermatologists and pathologists.

The Pathogenesis of Coronary Occlusion. By A. D. Morgan, M.D. (Pp. 170; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1956.

This study of one of the most important diseases which affects civilized man is divided into two parts—a historical review followed by a study of the morphology of coronary occlusion. We are reminded that the prevalence of coronary thrombosis was not widely accepted in England until 1926 and that the mortality from this disease in those over 35 has increased by fifteen times between 1921 and 1945. From his own detailed studies the author gives strong support to the view of Professor John Duguid that the most important pathological process is that of a clot, at first completely or partially obliterating the lumen of an artery, subsequently shrinking to one side of the vessel and later overgrown by endothelium. The pathological and biochemical processes involved are clearly set out and beautifully illustrated in a series of 179 figures and photomicrographs. The author and the publishers alike are to be congratulated on a very valuable contribution to this important subject.

Polymyositis. By John N. Walton, M.D., M.R.C.P., and Raymond D. Adams, M.D. (Pp. x+270; illustrated. 32s. 6d.) Edinburgh and London: E. & S. Livingstone, Ltd. 1958.

This collection of 40 cases within the experience of the authors, together with a summary of a large number of references, makes a very useful contribution to the study of general diseases and disorders of the voluntary muscles. Progressive muscular dystrophy and diseases unequivocally of infective origin are excluded from the survey, thus leaving a large heterogeneous group of muscle disorders which are at the present time known under different names such as dermatomyositis, generalized myositis ossificans, &c.

The present volume is a very useful account of the current position, well written and helpfully illustrated. It can be strongly recommended to neurologists, rheumatologists and all others interested in this difficult subject.

Fundamental Techniques of Plastic Surgery. By Ian A. McGregor, M.B., F.R.C.S.(Eng.), F.R.F.P.S.(Glas.). (Pp. viii+244; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone, Ltd. 1960.

This book is presented to bridge the gap between the advanced textbooks, which are said to pass over the elementary and fundamental methods of plastic surgery, and the sections on plastic surgery in more basic textbooks.

The first half of the book is altogether admirable, describing in quite sufficient detail all procedures which are gaining common acceptance by plastic surgeons and by all who are interested in the niceties of repair. A very satisfactory section on the use of free skin grafts is followed by good descriptions of the techniques and indications for the use of flaps, pedicles and tubes. All this section of the book is admirably illustrated, both by line drawings and by photographs.

The second part of the book, illustrating the applications of these techniques to general surgery, to orthopædic surgery and to hand surgery, is perhaps a little more ambitious than the simplicity of the beginning would appear to warrant. One can see difficulties arising where the apparent simplicity of procedure disguises its problems and it is not reasonable to suppose that in a book of this size all those problems can be dealt with. Nevertheless the author has admirably filled a long felt want and, provided that the reader's ambition is tempered with discretion, nothing but good can come from it.

One dose of 'Bimez' gives one day's 'Sulphamezathine' therapy

'BIMEZ', containing 'Sulphamezathine' and sulphadimethoxypyrimidine in the proportion of 3: 1, provides persistent sulphonamide blood levels which are maintained by single daily doses. It has also the outstanding advantages of safety and efficiency which have made 'Sulphamezathine' widely popular. This new, long-acting sulphonamide is available in two convenient dosage forms, Tablets and Suspension.

FEATURES

1. Absorption is rapid and complete as with 'Sulphamezathine'.
2. Effective blood levels.
3. Low toxicity.
4. Persistence, which makes single daily dosage practicable.

'Bimez' Tablets. Each tablet contains: 'Sulphamezathine' (Sulphadimidine B.P.) 0.375 gramme; sulphadimethoxypyrimidine 0.125 gramme. Issued in containers of 12, 50 and 500. Basic N.H.S. cost 12 tablets 3/8d. (5 day treatment for an adult).

'Bimez' Suspension. Especially suitable for children and the elderly. A teaspoonful (3.5 ml.) is equivalent to one tablet. Issued in bottles of 30 ml. Basic N.H.S. cost 4/- (5 day treatment for a child).

Bimez
TRADE MARK
(Tablets and Oral Suspension)

ICI

IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION
WILMSLOW CHESHIRE

Ph. 980

INDEX TO ADVERTISERS

PHARMACEUTICALS	PAGE
Allen & Hanburys Ltd.	xxix
Armour Pharmaceutical Co. Ltd.	xvi
Bayer Products Ltd.	*Inside back cover*
Beecham Research Laboratories Ltd.	xliv
Bengue & Co. Ltd.	xvii
Boots Pure Drug Co. Ltd.	xxxvii
Burroughs Wellcome & Co.	xxxix
Calmic Ltd.	xxxvi
Coates & Cooper Ltd.	xix
Distillers Co. (Biochemicals) Ltd.	x, xi
Glaxo Laboratories Ltd.	xxv
Imperial Chemical Industries Ltd.	li
Laboratories for Applied Biology Ltd.	xxiii
Leda Chemicals Ltd.	xiv
Lederle Laboratories Division (Cyanamid of Great Britain Ltd.)	xxvi, xxvii, xlii
Lilly, Eli & Co. Ltd.	xxii
Luitpold-Werk	xxxiii
Merck Sharp & Dohme Ltd.	xiii
Parke Davis & Co. Ltd.	xxviii, xlv
Pfizer Ltd. (C. H. Boehringer Sohn)	ii
Pharmaceutical Specialities (May & Baker) Ltd.	xli
Reckitt & Sons Ltd.	xxxv
Riddell Products Ltd.	xviii
Riker Laboratories Ltd.	xii, xxx, xxxi
Sandoz Products Ltd.	*Inside front cover*, xliii, xlvi
Searle, G. D., & Co. Ltd.	xl
Smith & Nephew Pharmaceuticals Ltd.	xxiv
Vitamins Ltd.	xxxii
Warner, William R., & Co. Ltd.	xv
Woolley, James Sons & Co. Ltd.	xvi
Wyeth, John & Brother Ltd.	*Outside back cover*

MEDICAL AND SURGICAL APPLIANCES	
Ames Company	xxxiv
Ilford Ltd.	xxxviii

FOODS AND DRINKS	
Hedges & Butler Ltd.	ix
Lucozade Ltd.	iv
Marmite Ltd.	ix
Walker, John & Sons Ltd.	viii

BOOKSELLERS AND PUBLISHERS	
Butterworth & Co. (Publishers) Ltd.	xlix
J. & A. Churchill Ltd.	vii
W. & G. Foyle Ltd.	viii
H.M.S.O.	viii
E. & S. Livingstone Ltd.	vii
Thomas Nelson & Sons Ltd.	vi
Pergamon Press Ltd.	xlviii
Pharmaceutical Press, The	v

MISCELLANEOUS	
Domestos Ltd.	xxi
G.V.D. Illuminators	xx
Medical Sickness Annuity and Life Assurance Society Ltd.	v
Medical Insurance Agency Ltd., The	ix
National Provincial Bank Ltd.	xx
St. Andrew's Hospital	xviii

MOTOR CARS	
Jaguar Cars	xlvii

PROCEEDINGS PRICE LIST

Copies of the whole *Proceedings* may be purchased through any bookseller or direct from the publishers. Prices are as follows:

Single copies	10s. 6d. each, post free (U.S.A. $2.00).
Annual subscription, covering 12 monthly issues and annual index	£6 6s. 0d. (U.S.A. $19.00).

Distributing Agents: H. K. Lewis & Co. Ltd., 136, Gower Street, London, W.C.1.

In the U.S.A.: Grune & Stratton, Inc., 381, Fourth Avenue, New York 16, N.Y., U.S.A.

Reprints of Sectional parts may be obtained direct from the Honorary Editors, Royal Society of Medicine, 1, Wimpole Street, London, W.1. Prices are as follows:—

Single copies	3s. 6d. each, post free.
Annual subscription	15s. 0d.

Fellows and Members of the Royal Society of Medicine are asked to apply direct to the Honorary Editors, Royal Society of Medicine, 1, Wimpole Street, London, W.1, for any copies of the *Proceedings* they may require, whether whole or Sectional, in addition to those they receive *gratis*. Prices to Fellows and Members are as follows:—

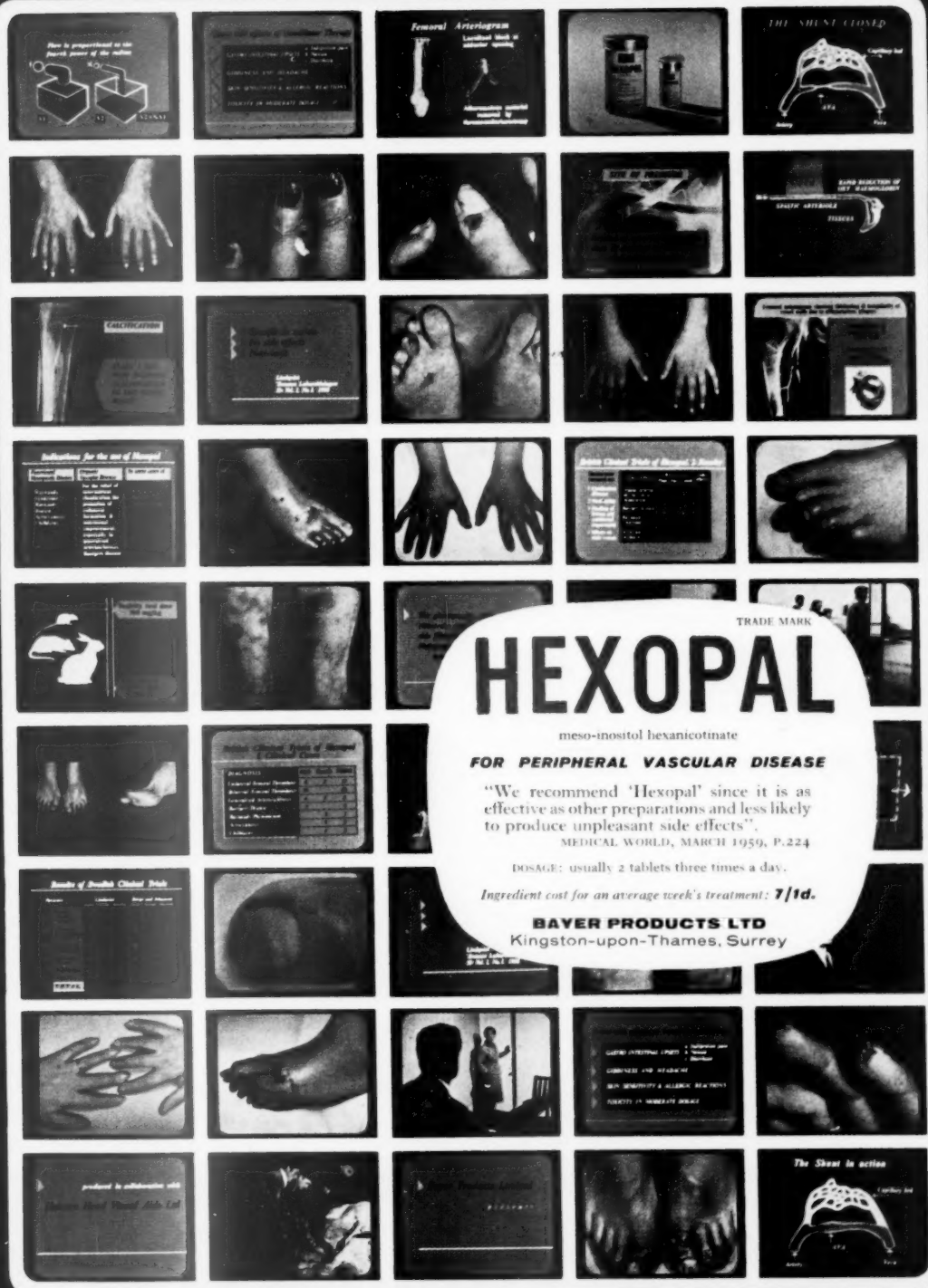
Whole *Proceedings:*

Single copies	7s. 6d. each, post free.
Complete volume (12 monthly issues and annual index)	£5 0s. 0d.

Sectional *Proceedings:*

Single copies	3s. 0d. each, post free.
Annual subscription	10s. 0d.

Printed in England by Staples Printers Limited, at their Great Titchfield Street, London, establishment.



TRADE MARK

HEXOPAL

meso-inositol hexanicotinate

FOR PERIPHERAL VASCULAR DISEASE

"We recommend 'Hexopal' since it is as effective as other preparations and less likely to produce unpleasant side effects".

MEDICAL WORLD, MARCH 1959, P.224

DOSAGE: usually 2 tablets three times a day.

Ingredient cost for an average week's treatment: **7/1d.**

BAYER PRODUCTS LTD

Kingston-upon-Thames, Surrey

This patient needs **Beplete**

Irritable, suspicious and resentful, she thinks she needs a tonic before she can set her world right. You know her need is for a sedative. Beplete* answers both demands. Tastefully, elegantly and economically, Beplete provides you with phenobarbitone disguised in a base of the vitamin B complex to counteract your patient's jaded appetite and to promote a feeling of well-being.

Available in elixir or tablet form. **trade mark*

Wyeth LONDON

Bpl/C/1